The binding sites of sulfonamides and salicylate to albumin were reported to be ε-amino moiety of the protein with an electrostatic interaction.[14] Thus, it may be considered that sulfamethoxazole and salicylate competitively bind to the same cationic binding sites on BSA.

Displacement of a drug from the binding sites on protein may change pharmacokinetic parameters of the drug and produce an increased pharmacologic effect as well as a toxic effect.

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14) I.M. Klotz, "The Proteins," Vol. 1, Academic press, New York, 1953.

[Chem. Pharm. Bull. 26(11)3576—3579(1978)]

UDC 547.722.5.04.09. : 615.281.011.5.015.11.076.7

Studies on Furan Derivatives. III.[1] Synthesis of 4-Substituted 5-(5-Nitro-2-furyl)thiazol-2-ones and Some of Their Derivatives

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Seven kinds of 4-substituted 5-(5-nitro-2-furyl)thiazol-2-ones were obtained by the reaction of α-substituted β-(5-nitro-2-furyl)vinylamines (Ia—g) with chlorocarbonylsulfenyl chloride. Reaction of Ia and c with trichloromethylsulfenyl chloride gave 3-substituted 4-(5-nitro-2-furyl)-5-chloroisothiazoles.

Keywords——nitrofuran derivatives; 5-(5-nitro-2-furyl)thiazol-2-ones; 2-chloro-5-(5-nitro-2-furyl)thiazoles; 4-(5-nitro-2-furyl)-5-chloroisothiazoles; cyclization of β-(5-nitro-2-furyl)vinylamines; antibacterial activity

A number of nitrofuran derivatives have hitherto been prepared with a view to obtaining antibacterial compounds. They may be grouped into three types with respect to their structure; (5-nitro-2-furyl)vinyls[3] (A), (5-nitro-2-furyl)azomethines[4] (B), and (5-nitro-2-furyl)heterocycles[5] (C).

Many compounds of type A exhibit higher antibacterial activity *in vitro* but the activity usually tends to decrease *in vivo*. Such a behavior is believed to be due to the instability

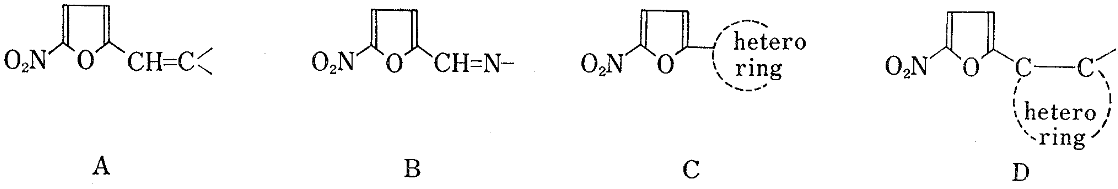

Chart 1

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1) Part II of this series, A. Tanaka, T. Usui, and S. Yoshina, *J. Heterocyclic Chem.*, **15**, 555 (1978).

2) Location: *Keyakidai, Sakado-shi, Saitama, Japan.*

3) H. Saikachi and A. Tanaka, *Yakugaku Zasshi*, **83**, 147 (1963); E.B. Akerblom, *J. Med. Chem.*, **17**, 609 (1974); Y. Lin, P.B. Hulbert, E. Bueding, and C.H. Robinson, *ibid.*, **17**, 835 (1974).

4) M.C. Dodd and W.B. Stillman, *J. Pharm. Expel. Therapy*, **82**, 11 (1944); E. Massaran, D. Nardi, A. Tajana, and L. Degen, *J. Med. Chem.*, **14**, 633 (1971); E. Szarvasi, *ibid.*, **16**, 281 (1973); C.F. Spencer, J.G. Michels, G.C. Wright, and C-H Yu, *ibid.*, **16**, 953 (1973).

5) W.R. Sherman, *J. Med. Chem.*, **8**, 25 (1965); S. Yoshina, I. Maeba, and K. Asai, *Yakugaku Zasshi*, **88**, 984 (1968); P.J. Islip and M.R. Johnson, *J. Med. Chem.*, **16**, 1308 (1973); H.A. Burch and L.E. Benjamin, *ibid.*, **17**, 451 (1974).

of the compounds of type A against some SH enzymes because it has been reported that the nitrofuran derivatives are unstable against cysteine and the stability of these compounds decreases in the order of A<B<C.[6]

In the present work, 4-substituted 5-(5-nitro-2-furyl)thiazol-2-ones were prepared from α-substituted β-(5-nitro-2-furyl)vinylamines[1,7] (Ia—g) as a new trial because of the interest of how the compounds of type D, adding across the olefinic bond in type A to form a heterocyclic ring, behave against microörganisms and cysteine.

Grohe and Heitzer[8] reported that the reaction of β-aminocrotonic esters with chlorocarbonylsulfenyl chloride (CSC) gave only thiazol-2-ones. First we tried the reaction of Ia—g with CSC in benzene. When Ia—g and CSC were stirred for 1 hr at 40—50° in benzene, a precipitate (IIa—g) was obtained in a good yield. The structures of IIa—g were confirmed from their various spectral data and elemental analyses. Next the reaction of Ia and Ic with trichloromethylsulfenyl chloride (TSC) in DMF was carried out, and yellow needles (IIIa) of mp 159—160.5° and yellow needles (IIIc) of mp 150—152° were obtained, respectively. The structures of IIIa and IIIc were considered to be 5-chloroisothiazoles or 2-chlorothiazoles from their elemental analyses and some spectral data.

On the other hand, Waite and Wooldridge[9] reported that the reaction of β-aminocrotonic esters with TSC gave 5-hydroxyisothiazoles. For further characterization of the structures of IIIa and IIIc, chlorination of IIa and IIc was carried out with a view to preparing 4-substituted 2-chloro-5-(5-nitro-2-furyl)thiazoles. Reaction of IIa with PCl_5 in $POCl_3$ gave orange needles (IVa) of mp 198.5—200°, in a low yield. Compound IVa was considered to have a dichloro structure because the mass spectral peak at *m/e* 330 (M^+) of IVa was different from that of the expected 2-chloro-4-(2-furyl)-5-(5-nitro-2-furyl)thiazole [*m/e* 295 (M^+)]. The nuclear magnetic resonance (NMR) spectra of IVa showed the following signals; two protons on the nitrofuran ring (7.30, 1H, d, $J=4$ Hz, 3 pos. and 7.53, 1H, d, $J=4$Hz, 4 pos.) and two protons on the furan ring (7.15, 1H, d, $J=3.6$ Hz, 4 pos. and 6.45, 1H, d, $J=3.6$ Hz, 3 pos.). The relation between 3-H and 4-H on the nitrofuran ring was confirmed by the spin-spin decoupling method. Thus, it is reasonable to assume that the structure of IVa would be 2-chloro-4-(5-chloro-2-furyl)-5-(5-nitro-2-furyl)thiazole. Moreover, the elemental analytical value of IVa agreed with a molecular formula of $C_{11}H_4Cl_2N_2O_4S$. Although the mechanism of the chlorination of the furan ring is at present unknown, we assume that the reaction is due to Cl_2 possibly produced by oxidation of HCl with the nitrofuran moiety.

Similarly, the reaction of IIc with PCl_5 in $POCl_3$ gave yellow needles (IVc) of mp 161—162° in 60% yield. Both IVc and IIIc gave the same mass spectral peak at *m/e* 340 (M^+) but the

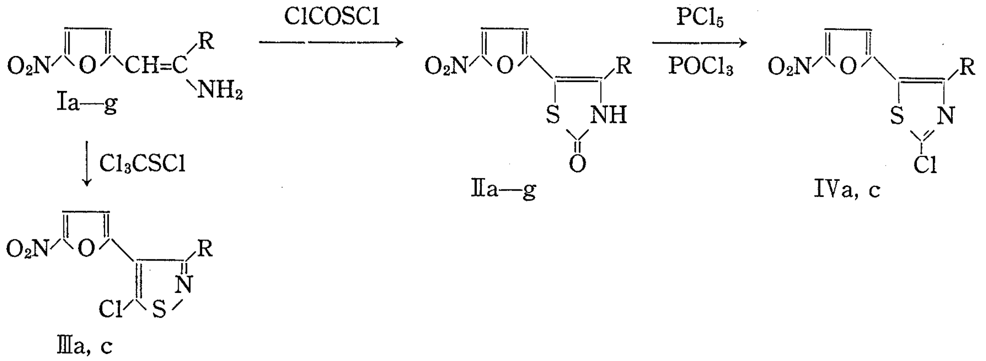

Chart 2

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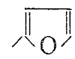
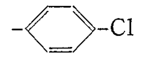
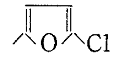
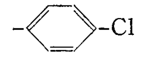
[6] H. Fujioka, Y. Nakanishi, and K. Nakamura, *Yakugaku Zasshi*, **93**, 570 (1973).
[7] S. Yoshina, A. Tanaka, and T. Usui, *Yakugaku Zasshi*, **97**, 1007 (1977); *idem, ibid.*, **98**, 286 (1978).
[8] K. Grohe and H. Heitzer, *Liebigs Ann. Chem.*, **1973**, 1018.
[9] J.A. Waite and K.R.H. Wooldridge, *Tetrahedron Lett.*, **1972**, 327.

Table I. The Spectral Data of IIIa, IIIc, IVa, and IVc

Compd. No.	R	MS (M^+)	UV λ_{max}^{EtOH} nm	NMR[a] (in $CDCl_3$)
IIIa		296	293 346	6.58 (1H, d-d, $J=1.8$ Hz, $J=3.8$ Hz, F ring proton 4 pos.), 7.55 (2H, m, F ring proton 5 pos. and NF ring proton 4 pos.), 6.88 (2H, m, F ring proton 3 pos. and NF ring proton 3 pos.)
IIIc		340	276 329	6.72 (1H, d, $J=4$ Hz, NF ring proton 3 pos.), 7.50 (5H, broad s, NF ring proton 4 pos. and phenyl protons)
IVa		330	305 396	7.53 (1H, d, $J=4$ Hz, NF ring proton 4 pos.), 7.30 (1H, d, $J=4$ Hz, NF ring proton 3 pos.), 7.15 (1H, d, $J=3.6$ Hz, F ring proton 4 pos.), 6.45 (1H, d, $J=3.6$ Hz, F ring proton 3 pos.)
IVc		340	242 380	6.45 (1H, d, $J=4$ Hz, NF ring proton 3 pos.), 7.28 (1H, d, $J=4$ Hz, NF ring proton 4 pos.), 7.48 (2H, d, $J=9$ Hz, phenyl protons), 7.55 (2H, d, $J=9$ Hz, phenyl protons)

a) s: singlet, d: doublet, d-d: double doublet, m: multiplet, F: furan, NF: nitrofuran.

fragmentation of IVc was different from that of IIIc. The spectral data of IIIa, IIIc, IVa, and IVc are shown in Table I.

These data suggest that the structure of IIIa and IIIc is a 3-substituted 4-(5-nitro-2-furyl)-5-chloroisothiazole, and the characteristic absorption band in their ultraviolet (UV) spectra supported this assumption; the maximum absorption of thiazole structures (IVa and IVc) shifted to a longer wavelength region compared with that of isothiazole structures (IIIa and IIIc).

As mentioned above, it was found that the reaction of β-(5-nitro-2-furyl)vinylamines with CSC gave 5-(5-nitro-2-furyl)thiazol-2-ones and that with TSC gave 4-(5-nitro-2-furyl)-5-chloroisothiazoles.

The derivatives IIa—g were tested for their antibacterial activity and they exhibited little biological activity, with the exception of IIb and IIc which showed activity against *Streptococcus hemolyticus* and *Staphylococcus aureus* (minimum inhibitory concentration, 1.65—12.5 μg/ml).

Experimental

All melting points are uncorrected. The following instruments were used for obtaining the physical data. NMR spectra (TMS as internal standard): JEOL-60HL and PS-100; IR spectra; JASCO IRI-1; UV spectra: JASCO UVIDEC-1; mass spectra (direct solid inlet): Shimadzu LKB-9000. Column chromatography was carried out on silica gel (Wako gel C-200). Trichloromethylsulfenyl chloride was purchased from Tokyo Chemical Industry Co., LTD. and chlorocarbonylsulfenyl chloride was prepared by hydrolysis of trichloromethylsulfenyl chloride.[10]

4-Substituted 5-(5-Nitro-2-furyl)thiazol-2-ones (IIa—g)——To a stirred solution of Ia—g (0.002 mol) in 50 ml of benzene, 0.26 g (0.002 mol) of CSC was portionwise added under cooling in ice bath. After the addition, the mixture was heated at 40—50° for 1 hr. The precipitate was filtered and recrystallized from suitable solvents to give IIa—g. NMR (in DMSO-d_6): IIa; 7.03 (1H, d, $J=4$ Hz, nitrofuran ring proton 3 pos.), 7.83 (1H, d, $J=4$ Hz, nitrofuran ring proton 4 pos.), 6.80 (1H, q, $J=2$ Hz, $J=3.8$ Hz, furan ring proton 4 pos.), 7.27 (1H, d, $J=3.8$ Hz, furan ring proton 3 pos.), 8.00 (1H, d, $J=2$ Hz, furan ring proton 5 pos.), IIc; 6.47 (1H, d, $J=4$ Hz, nitrofuran ring proton 3 pos.), 7.75 (1H, d, $J=4$ Hz, nitrofuran ring proton 4 pos.), 7.70 (4H, s, phenyl protons).

3-(2-Furyl)-4-(5-nitro-2-furyl)-5-chloroisothiazole (IIIa)——A mixture of 0.44 g (0.002 mol) of Ia, 0.37 g (0.002 mol) of TSC and 20 ml of DMF was stirred for 48 hr at room temperature. The mixture was poured into ice water and extracted with benzene. The benzene extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene as eluent to give IIIa (70 mg,

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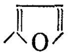
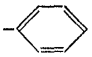
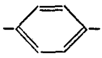
[10] Bayer AG, *Neth. Appl.* 6514548 (1966) [*C.A.*, **65**, 12112 (1966)].

Table II. The Physical and Spectral Data of IIa—g

Compd. No.	R	IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: C=O	MS (M$^+$)	UV $\lambda_{\max}^{\text{EtOH}}$ nm	mp (°C)	Yield (%)	Solvent	Formula	Analysis (%) Calcd. (Found)		
									C	H	N
IIa		1675	278	303 419	235— 237	71	Acetone	$C_{11}H_6N_2O_5S$	47.49 (47.44	2.17 2.01	10.07 9.95)
IIb	-	1675	288	284 406	209	57	MeOH	$C_{13}H_8N_2O_4S$	54.17 (54.33	2.80 2.54	9.72 9.66)
IIc	--Cl	1660	322	287 402	253— 255	66	Acetone	$C_{13}H_7ClN_2O_4S$	48.39 (48.30	2.19 2.19	8.68 8.45)
IId	--Br	1660	366	284 400	259— 261	59	Ethyl-acetate	$C_{13}H_7BrN_2O_4S$	42.53 (42.30	1.92 2.03	7.63 7.43)
IIe	--I	1665	414	290 402	240 (dec.)	72	Ethyl-acetate	$C_{13}H_7IN_2O_4S$	37.70 (37.42	1.70 1.88	6.77 6.44)
IIf	--OCH$_3$	1660	318	290 413	243— 245	83	MeOH	$C_{14}H_{10}N_2O_5S$	52.83 (52.62	3.17 3.05	8.80 8.68)
IIg	--NO$_2$	1670	333	260 401	232— 234	33	Ethyl-acetate	$C_{13}H_7N_3O_6S$	46.86 (46.52	2.12 2.31	12.61 12.43)

12%) as yellow needles, mp 159—160.5° (from MeOH). *Anal.* Calcd. for $C_{11}H_5ClN_2O_4S$: C, 44.54; H, 1.70; N, 9.45. Found: C, 44.33; H, 1.68; N, 9.63.

3-(*p*-Chlorophenyl)-4-(5-nitro-2-furyl)-5-chloroisothiazole (IIIc)——The procedure was identical with that used in the preparation of IIIa. In this manner, IIIc (100 mg, 15%) as yellow needles, mp 150—152° (from EtOH), was synthesized from 0.53 g (0.002 mol) of Ic. *Anal.* Calcd. for $C_{13}H_6Cl_2N_2O_3S$: C, 45.77; H, 1.77; N, 8.21. Found: C, 45.48; H, 1.93; N, 8.30.

2-Chloro-4-(5-chloro-2-furyl)-5-(5-nitro-2-furyl)thiazole (IVa)——A mixture of 0.56 g (0.002 mol) of IIa, 0.83 g (0.004 mol) of PCl_5 and 10 ml of $POCl_3$ was refluxed for 3 hr. The mixture was poured into ice water and extracted with benzene. The benzene extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene as eluent to give IVa (40 mg, 6%) as orange needles, mp 198.5—200° (from ligroin). *Anal.* Calcd. for $C_{11}H_4Cl_2N_2O_4S$: C, 39.90; H, 1.22; N, 8.46. Found: C, 39.65; H, 1.21; N, 8.56.

2-Chloro-4-(*p*-chlorophenyl)-5-(5-nitro-2-furyl)thiazole (IVc)——The procedure was identical with that used in the preparation of IVa. In this manner, IVc (410 mg, 60%) as yellow needles, mp 161—162° (from EtOH), was synthesized from 0.64 g (0.002 mol) of IIc. *Anal.* Calcd. for $C_{13}H_6Cl_2N_2O_3S$: C, 45.77; H, 1.77; N, 8.21. Found: C, 45.73; H, 1.79; N, 8.19.

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