[Chem. Pharm. Bull. 29(3) 635—645 (1981)]

Synthesis and Antimicrobial Activity of Methyl 5-Nitro-3,4-diphenylfuran-2-carboxylate and Related Compounds

Sheng-Chu Kuo,*,[a] Chun-Hsiung Wu,[a] Li-Jiau Huang,[a] Katsumi Yamamoto,[b] and Shigetaka Yoshina (the late)[c]

School of Pharmacy, China Medical College,[a] Taichung 400, Taiwan, Republic of China, Faculty of Pharmaceutical Sciences, Josai University,[b] Keyakidai 1-1, Sakado-shi, Saitama, 350-02, Japan, and Faculty of Pharmacy, Meijo University,[c] Tempaku-cho, Tempaku-ku, Nagoya, Japan

(Received August 26, 1980)

In order to investigate the antimicrobial activity of derivatives of methyl 5-nitro-3,4-diphenylfuran-2-carboxylate, we first studied the optimal conditions for the nitration of methyl 3,4-diphenylfuran-2-carboxylate. Starting from the nitrofuran methyl ester, various amides, hydrazides, hydrazones, oxadiazoles and thiazoles were synthesized and examined for antimicrobial activity. Most of the derivatives were active against *T. vaginalis*.

Keywords——nitration; diphenylfuran derivatives; mononitrodiphenylfuran derivatives; trinitrodiphenylfuran derivatives; antimicrobial activity; *T. vaginalis*

Most of the commercially available nitrofurans are synthesized from nitrofurfural. In our investigation of the biological activity of 3,4-diphenyl-5-nitrofurans, the corresponding aldehyde was also used as a starting material for the synthesis of Schiff bases and vinylene-type derivatives.[1,2] Some of these derivatives were found to possess very strong antimicrobial activity and among them, some compounds showed broadspectrum antimicrobial activities. However, the relationship between oxidation–reduction potential and antimicrobial activity of nitrofuran derivatives did not coincide with that of 3,4-diphenyl-5-nitrofuran derivatives. Therefore, we were interested in further examination of the antimicrobial activity of 3,4-diphenyl-5-nitrofurans. In this work, an ester, methyl 5-nitro-3,4-diphenyl-2-carboxylate (**3**), was chosen as a versatile key intermediate for the synthesis of a series of derivatives for examination of their antimicrobial activities. The conditions offering maximum yield of the key intermediate were also investigated.

Chemistry

Nitration of Methyl 3,4-Diphenylfuran-2-carboxylate (1)——Since both the 5 position of the furan ring and the *para* positions of the phenyl groups are susceptible to nitration we tried several nitration methods and quantified the products by high performance liquid chromatography (HPLC) in order to ascertain the relative reactivities of the three active positions.

Method A: The standard process for furan nitration was as follows. Compound **1** was added to acetyl nitrate at low temperature and two products were obtained. One melted at 159—161° (dec.) (**2**), and the other melted at 171—173° (**3**). Based on the mass spectrum (MS) (M^+ 383) and elemental analysis, the molecular formula of the former compound was determined as $C_{20}H_{17}NO_7$, which indicated that it could be an acetine intermediate formed during nitration. The infrared (IR) spectrum of **2** showed two carbonyl absorptions at 1700, 1770 cm^{-1} and absorptions at 1350, 1560 cm^{-1} due to the nitro group. The nuclear magnetic resonance (NMR) spectrum exhibited two methyl groups [δ 2.30 (s), δ 3.50 (s)], a phenyl group δ 7.20—7.40 (m) and a singlet at δ 7.70 which was assigned to the proton at the 5 position of the dihydrofuran ring. From the above data, compound **2** was confirmed to be an intermediate of acetine type, methyl 2-acetoxyl-5-nitro-3,4-diphenyl-2,5-diphydrofuran-2-carboxylate (**2**). The other compound **3** was concluded to be the desired product, methyl 5-nitro-3,4-diphenyl-

furan-2-carboxylate from its spectral data and elemental analysis. When compound **2** was treated with pyridine or heat, acetic acid was lost from the molecule to afford compound **3**. Finally, the effect of temperature on the yield was checked. The results are shown in Table V.

Method B: To minimize the formation of by-products, we modified method A by suspending **1** in Ac_2O and adding acetyl nitrate dropwise. As expected, the yields of **2** and **3** were improved.

Method C: Saikachi *et al.*[3] reported that the use of conc. H_2SO_4 as a catalyst during nitration of furan derivatives can increase the yield. When method A was used with the addition of conc. H_2SO_4 as a catalyst, the products obtained were different from those of method A. In this case, the products melted at 223—225° (dec.) (**4**) and 244—246° (**5**). The molecular formula of the former was determined as $C_{20}H_{15}N_3O_{11}$ based upon its MS (M^+ 473) and elemental analysis. It appears that there are two additional nitro groups in **4** compared with **2**. The IR spectrum showed two carbonyl absorptions at 1770, 1700 cm^{-1} and nitro group absorptions at 1350, 1560 cm^{-1}. The NMR spectrum exhibited two methyl groups at δ 2.32 (3H, s) and δ 3.52 (3H, s). The signals at δ 7.50—7.70 (4H, m) and δ 8.10—8.30 (5H, m) were assigned to the aromatic protons on the nitrophenyl rings and H_5 on the dihydrofuran ring. From the above-mentioned data, it was clear that compound **4** was acetine type and contained three nitro groups. However, the positions of the nitro groups on the two phenyl rings could not be assigned. When compound **4** was treated with pyridine, a product with mp 244—246° was obtained and was proved to be the same compound as the nitration product **5**. The NMR spectrum showed a methyl group at δ 3.85 (3H, s) and the four sets of doublets at δ 7.48 (2H, d, J=9.0 Hz), δ 7.58 (2H, d, J=9.0 Hz), δ 8.18 (2H, d, J=9.0 Hz) and δ 8.22 (2H, d, J=9.0 Hz) were assigned to the aromatic protons on the two nitrophenyl rings. These A_2B_2 type slpittings indicated that the substitution patterns on the rings were *para*. The structure of compound **5** was confirmed to be methyl 5-nitro-3,4-bis(*p*-nitrophenyl)furan-2-carboxylate according to the spectral data and elemental analysis. Accordingly, the nitro groups on the phenyl rings of compound **4** can be assigned to the *para* positions. Product **3** cannot be obtained by method C at lower temperature, as shown in Table V.

Method D: Method B was modified by the addition of a trace of conc. H_2SO_4. The results shown in Table V are essentially the same as those of method C.

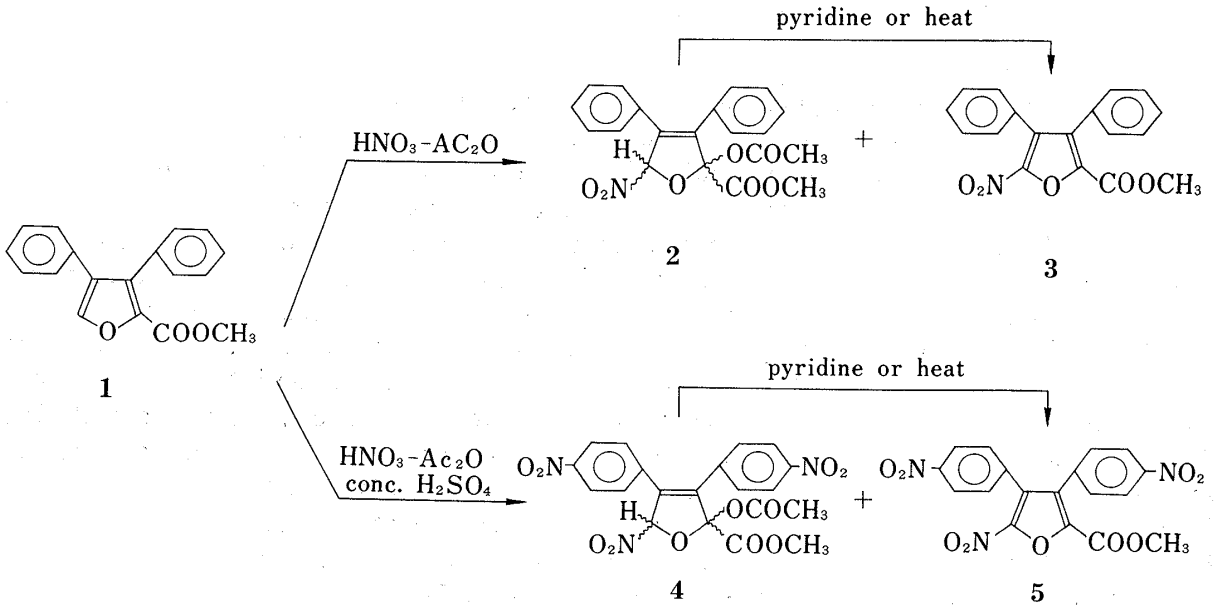


Chart 1

From the above studies, we found that the nitration of **1** can afford higher yields of compounds **2** and **3** under milder conditions (*e.g.* Method B, −30 to −40°), and the presence of conc. H_2SO_4 can also cause nitration at the *para* positions of the two phenyl rings.

5-Nitro-3,4-diphenyl-N-substituted-2-furamides (8)——As Chart 2 shows, when compound **3** was hydrolyzed at room temperature, 5-nitro-3,4-diphenylfuran-2-carboxylic acid (**6**) was obtained in good yield. Compound **6** was allowed to react with $SOCl_2$ to afford 5-nitro-3,4-diphenyl-2-furoyl chloride (**7**), which was treated with a variety of aliphatic and aromatic amines to give corresponding amides **8** (Table I).

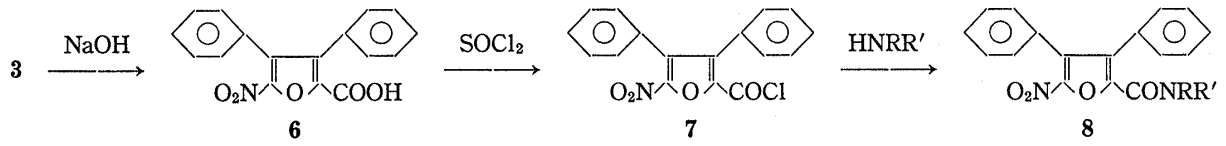
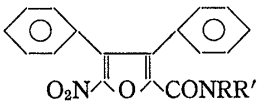
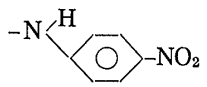
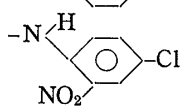
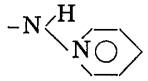
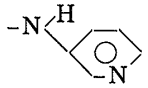
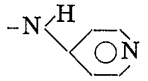
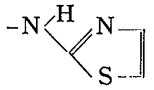
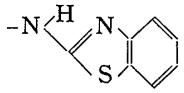
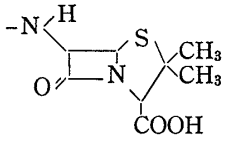


Chart 2

Table I. 5-Nitro-3,4-diphenyl-N-substituted-2-furamides (**8a—w**)



Compd.	$-N\langle^{R}_{R'}$	mp (°C)	Recrystn. solvent	Yield (%)	Formula[a]	Analysis(%) Calcd (Found) C	H	N
8a	$-NH_2$	237—239	EtOH	63	$C_{17}H_{12}N_2O_4$	66.23 (66.00	3.91 3.76	9.09 9.15)
8b	$-N\langle^{H}_{CH_3}$	184—186	EtOH	57	$C_{18}H_{14}N_2O_4$	67.07 (66.95	4.38 4.01	8.69 9.02)
8c	$-N\langle^{H}_{CH_2CH_3}$	170—172	MeOH	60	$C_{19}H_{16}N_2O_4$	67.85 (67.53	4.80 4.68	8.33 8.32)
8d	$-N\langle^{H}_{n\text{-}C_3H_7}$	158—160	MeOH	74	$C_{20}H_{18}N_2O_4$	68.56 (68.36	5.18 5.22	8.00 7.88)
8e	$-N\langle^{H}_{iso\text{-}C_3H_7}$	159—161	MeOH	78	$C_{20}H_{18}N_2O_4$	68.56 (68.82	5.18 5.10	8.00 8.06)
8f	$-N\langle^{CH_2}_{CH_2}$	178—180	MeOH	80	$C_{19}H_{14}N_2O_4$	68.25 (68.21	4.22 4.10	8.37 7.98)
8g	$-N\langle^{H}_{C_6H_5}$	164—166	MeOH	84	$C_{23}H_{22}N_2O_4$	70.75 (71.08	5.68 5.54	7.18 7.13)
8h	$-N\langle^{H}_{NHCONH_2}$	180—181 (dec.)	MeOH	63	$C_{18}H_{14}N_4O_5$	59.02 (59.31	3.85 3.67	15.29 15.52)
8i	$-N\langle^{H}_{NHCSNH_2}$	191—192 (dec.)	EtOH	60	$C_{18}H_{14}N_4O_4S$	56.54 (56.30	3.69 3.90	14.65 14.91)
8j	$-N\langle^{H}_{C_6H_5}$	218—219	MeOH–dioxane	85	$C_{23}H_{16}N_2O_4$	71.87 (71.85	4.20 4.00	7.29 7.52)
8k	$-N\langle^{H}_{C_6H_4\text{-}CH_3}$	223—225	MeOH–dioxane	67	$C_{24}H_{18}N_2O_4$	72.35 (72.01	4.55 4.35	7.03 7.31)
8l	$-N\langle^{H}_{C_6H_4\text{-}OCH_3}$	246—248	Benzene	79	$C_{24}H_{18}N_2O_5$	69.56 (69.77	4.38 4.20	6.76 6.93)
8m	$-N\langle^{H}_{C_6H_4\text{-}OCH_2CH_3}$	218—219	Benzene	76	$C_{25}H_{20}N_2O_5$	70.08 (70.32	4.71 4.44	6.54 6.91)
8n	$-N\langle^{H}_{C_6H_4\text{-}Cl}$	248—250	MeOH–dioxane	70	$C_{23}H_{15}ClN_2O_4$	66.02 (66.01	3.60 3.51	6.69 6.77)
8o	$-N\langle^{H}_{C_6H_4\text{-}COOH}$	265—267	Dioxane–H_2O	76	$C_{24}H_{16}N_2O_6$	67.29 (67.45	3.76 3.60	6.54 6.09)

Compd.	$-N\langle^{R}_{R'}$	mp (°C)	Recrystn. solvent	Yield (%)	Formula[a]	Analysis (%) Calcd (Found) C	H	N
8p		181—183 (dec.)	EtOH	69	$C_{23}H_{15}N_3O_6$	64.33 (64.74	3.52 3.25	9.79 9.67)
8q		182—183 (dec.)	EtOH	30	$C_{23}H_{14}ClN_3O_6$	59.56 (59.56	3.04 3.31	9.06 9.15)
8r		205—207	EtOH	23	$C_{22}H_{15}N_3O_4$	68.56 (68.75	3.92 3.69	10.91 11.02)
8s		220—222	EtOH	70	$C_{22}H_{15}N_3O_4$	68.56 (68.59	3.92 3.90	10.91 10.76)
8t		217—219	EtOH	77	$C_{22}H_{15}N_3O_4$	68.56 (68.41	3.92 3.99	10.91 10.69)
8u		223—225	MeOH	73	$C_{20}H_{13}N_3O_4S$	61.38 (61.04	3.32 3.56	10.74 10.50)
8v		240—242	Dioxane	80	$C_{24}H_{15}N_3O_4S$	65.30 (65.51	3.40 3.05	9.52 9.72)
8w		270—271 (dec.)	Acetone	60	$C_{25}H_{21}N_3O_7S$	59.17 (59.00	4.17 4.34	8.28 8.03)

a) All compounds were analyzed for, C, H and N; analytical results were within ± 0.3% of the theoretical values.

5-Nitro-3,4-diphenyl-2-furoylhydrazones (11)——5-Nitro-2-furoylhydrazine[4] can be easily obtained by mixing methyl 5-nitro-2-furoate with hydrazine hydrate under cooling and by using methanol as an additional solvent. We failed to obtain 5-nitro-3,4-diphenyl-2-furoylhydrazine (**9**) by a similar procedure. However, when the acid chloride **7** was used as the starting material and allowed to react with excess hydrazine hydrate at low temperature, compound **9** was isolated together with the diacylhydrazine N,N′-bis(5-nitro-3,4-diphenyl-2-furoyl)hydrazine (**10h**). Compound **9** was then reacted with a variety of lower aliphatic aldehydes or ketones to afford corresponding hydrazones (**11**), as shown in Table II.

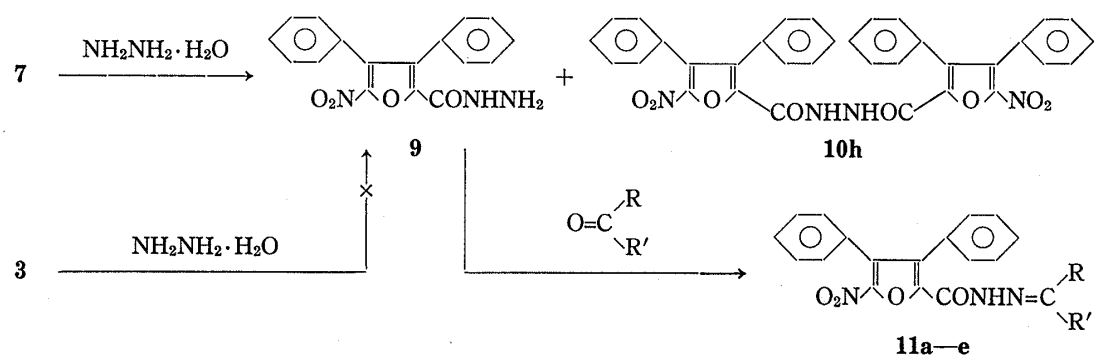
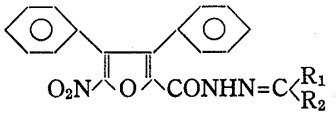


Chart 3

Table II. 5-Nitro-3,4-diphenyl-2-furoylhydrazone (11)



Compd.	$=C\langle^{R_1}_{R_2}$	mp(°C)	Recrystn. solvent	Yield (%)	Formula[a]	Analysis(%) Calcd (Found) C	H	N
11a	$=C\langle^{CH_3}_{CH_3}$	238—240	Acetone	78	$C_{20}H_{17}N_3O_4$	66.11 (65.92	4.72 4.37	11.57 11.52)
11b	$=C\langle^{H}_{CH_3}$	212—214	EtOH	81	$C_{19}H_{15}N_3O_4$	65.32 (65.70	4.33 4.37	12.03 12.34)
11c	$=C\langle^{H}_{CH_2CH_3}$	208—210	EtOH	78	$C_{20}H_{17}N_3O_4$	66.11 (66.25	4.72 4.60	11.57 11.67)
11d	$=C\langle^{H}_{n\text{-}C_3H_7}$	162—164	EtOH	80	$C_{21}H_{19}N_3O_4$	66.83 (66.72	5.07 5.09	11.14 11.23)
11e	$=C\langle^{H}_{i\text{-}C_3H_7}$	156—158	EtOH	76	$C_{21}H_{19}N_3O_4$	66.83 (66.95	5.07 5.19	11.14 11.25)

a) All compounds were analyzed for C, H and N; analytical results were within ± 0.3% of the theoretical values.

2-[5-Nitro-3,4-diphenyl-2-furyl]-5-substituted-1,3,4-oxadiazoles (12)——As shown in Chart 4, compound **7** was treated with acylhydrazines in the presence of pyridine to afford the corresponding N-(5-nitro-3,4-diphenyl-2-furoyl)-N′-acylhydrazines (**10a—h**), which were then treated with $POCl_3$ to give oxadiazoles (**12a—h**). For the synthesis of 2-amino-5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazole (**12i**), we applied the method of Sherman[5] to treat **9** with cyanogen bromide in methanol. Saikawa's method[6] was followed to treat **12i** with formaldehyde in DMF to furnish 2-[bis(hydroxy-methyl)amino]-5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazoles (**12j**). The related compounds, 5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,-4-oxadiazol-2-one (**13**) and 5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazole -2-thione(**14**), were synthesized by application of Sherman's[5] method, by allowing compound **9** to react with phosgene and thiophosgene, respectively.

2-(5-Nitro-3,4-diphenyl-2-furyl)-5-substituted Thiazole (17)——Sherman[7] used the nitrile as a starting material to synthesize nitrofuran derivatives. As indicated in Chart 5, the

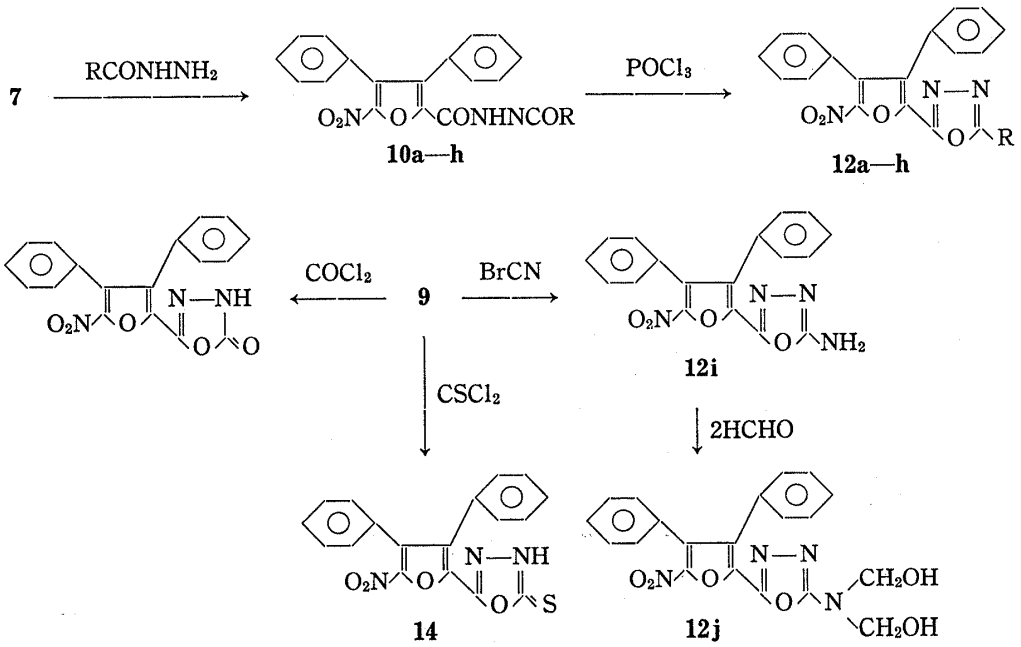
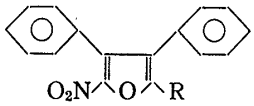
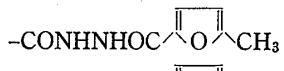
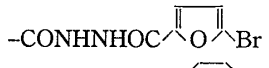
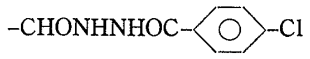
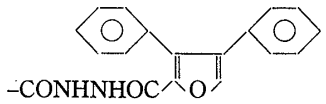
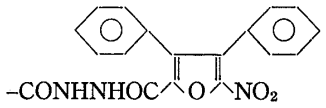
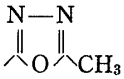
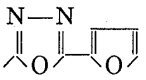
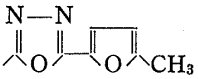
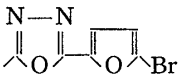
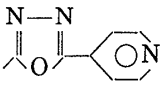
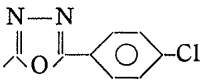
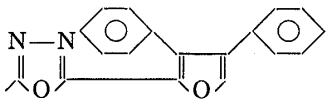
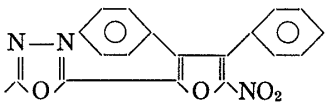
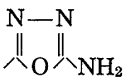
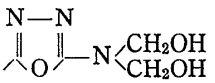


Chart 4

TABLE III. 2-Substituted-5-nitro-3,4-diphenylfuran (**11**, **12**)



Compd.	R	mp(°C)	Recrystn. solvent	Yield (%)	Formula[a]	Analysis (%) Calcd (Found) C	H	N
10a	$-CONHNHOCCH_3$	204—205	MeOH	78	$C_{19}H_{15}N_3O_5$	62.46 (62.61	4.14 4.19	11.50 11.24)
10b		178—180	MeOH	73	$C_{22}H_{15}N_3O_6$	63.31 (63.05	3.62 3.64	10.07 9.82)
10c		163—164 (dec.)	Benzene	71	$C_{23}H_{17}N_3O_6$	64.03 (63.78	3.97 3.78	9.74 9.56)
10d		120—121 (dec.)	Benzene	52	$C_{22}H_{14}BrN_3O_6$	53.24 (53.61	2.84 2.54	8.46 8.14)
10e		163—165 (dec.)	MeOH–H_2O	56	$C_{23}H_{16}N_4O_5$	64.48 (64.97	3.76 3.75	13.08 12.81)
10f		200—202	EtOH	61	$C_{24}H_{16}ClN_3O_5$	62.33 (62.81	3.46 3.55	9.09 8.92)
10g		238—240	Dioxane–MeOH	50	$C_{34}H_{23}N_3O_6$	71.70 (71.42	4.07 3.86	7.38 7.42)
10h		248—249 (dec.)	Dioxane–MeOH	61	$C_{34}H_{22}N_4O_8$	66.45 (66.23	3.61 3.58	9.13 9.22)
12a		192—194	Dioxane–MeOH	90	$C_{19}H_{13}N_3O_4$	65.70 (65.50	3.77 3.50	12.10 12.11)
12b		208—210	Dioxane–MeOH	72	$C_{22}H_{13}N_3O_5$	66.16 (65.94	3.28 3.06	10.52 10.41)
12c		215—217	Dioxane–H_2O	66	$C_{23}H_{15}N_3O_5$	66.63 (66.82	3.66 3.79	10.17 10.26)
12d		241—243	Dioxane–H_2O	70	$C_{22}H_{13}BrN_3O_5$	55.23 (55.19	2.51 2.40	8.78 8.51)
12e		218—220 (dec.)	Dioxane–MeOH	35	$C_{23}H_{14}N_4O_4$	67.31 (67.44	3.44 3.47	13.65 13.62)
12f		218—219	Dioxane–MeOH	80	$C_{24}H_{14}ClN_3O_4$	65.00 (64.57	3.16 3.00	9.48 9.26)
12g		238—240	Dioxane	80	$C_{34}H_{21}N_3O_5$	74.04 (73.80	3.84 3.49	7.62 7.33)
12h		245—247 (dec.)	Dioxane	70	$C_{34}H_{20}N_4O_7$	68.46 (68.27	3.38 3.59	9.39 9.21)
12i		232—234	EtOH	75	$C_{18}H_{12}N_4O_4$	62.07 (62.35	3.47 3.80	16.09 16.00)
12j		220—221 (dec.)	EtOH	62	$C_{20}H_{16}N_4O_6$	58.82 (58.90	3.95 4.02	13.72 13.51)

a) All compounds were analyzed for C, H and N; analytical results were within ± 0.3% of the theoritical values.

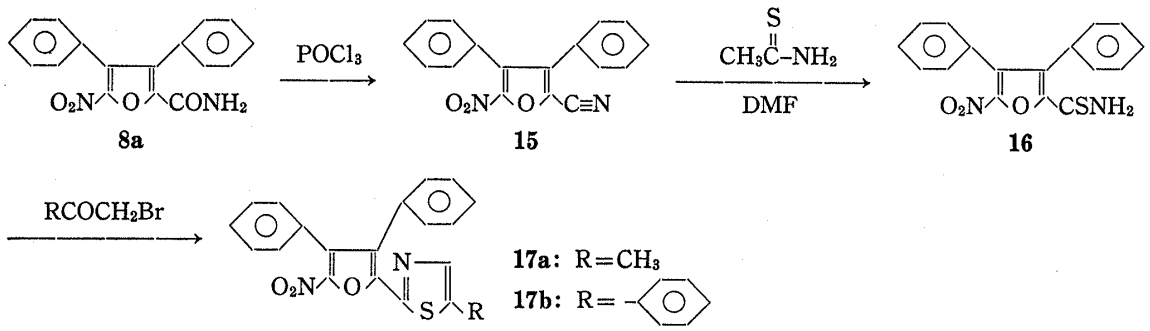


Chart 5

TABLE IV. *In Vitro* Antimicrobial Activity (Incubation Time, 48 hr; Minumum Inhibitory Concentration, μg/ml)

Compd.	*S. aureus*[a]	*E. coli*[b]	*S. flex.*[c]	*P. aeru*[d]	*C. albi*[e]	*T. menta*[f]	*T. vagi*[g]	*M. tuber*[h]
8a	>30	>30	>30	>30	>30	>30	30	>30
8b	>30	>30	>30	>30	>30	>30	30	>30
8c	>30	>30	>30	>30	>30	>30	30	>30
8f	>30	>30	>30	>30	>30	>30	30	>30
8g	>30	>30	>30	>30	>30	>30	30	>30
8h	>30	>30	>30	>30	>30	>30	10	>30
8i	>30	>30	>30	>30	>30	>30	10	>30
8j	>30	>30	>30	>30	>30	>30	10	>30
8k	>30	>30	>30	>30	>30	>30	30	>30
8l	>30	>30	>30	>30	>30	>30	30	>30
8n	>30	>30	>30	>30	>30	>30	30	>30
8o	>30	>30	>30	>30	>30	>30	30	>30
8s	>30	>30	>30	>30	>30	>30	30	>30
8t	>30	>30	>30	>30	>30	>30	30	>30
8w	25	>30	>30	>30	>30	>30	>30	>30
9	1	>30	>30	>30	>30	>30	30	30
10a	10	>30	>30	>30	>30	>30	30	30
10b	1	>30	>30	>30	>30	>30	10	10
10c	3	>30	>30	>30	>30	>30	30	10
10d	3	>30	>30	>30	>30	>30	10	10
10e	10	>30	>30	>30	>30	>30	30	>30
10f	>30	>30	>30	>30	>30	>30	30	10
10h	3	>30	>30	>30	>30	>30	>30	>30
11a	10	>30	>30	>30	>30	>30	30	>30
11b	10	>30	>30	>30	>30	>30	30	>30
11c	10	>30	>30	>30	>30	>30	30	30
11d	>30	>30	>30	>30	>30	>30	30	30
11e	>30	>30	>30	>30	>30	>30	30	>30
12a	>30	>30	>30	>30	>30	>30	30	>30
12h	>30	>30	>30	>30	>30	>30	30	>30
12i	1	>30	>30	>30	>30	>30	10	30
12j	1	>30	>30	>30	>30	>30	30	30
13	>30	>30	>30	>30	>30	>30	30	>30
14	>30	>30	>30	>30	>30	>30	30	>30
15	3	>30	>30	>30	>30	>30	10	10
16	3	>30	>30	>30	>30	>30	30	>30
17a	>30	>30	>30	>30	>30	>30	30	>30
Nitrofurazone	10	10	3	>30				

a) *Staphylococcus aureus* Terajima.
b) *Escherichia coli* K-12.
c) *Shigella flexneri.*
d) *Pseudomonas aeruginosa.*
e) *Candida albicans.*
f) *Trichephyton mentabrophytes.*
g) *Trichomonas vaginalis.*
h) *Myobacterium tuberculosis.*

amide **8a** was treated with $POCl_3$ to furnish 5-nitro-3,4-diphenyl-2-furonitrile (**15**), which was subsequently reacted with thioacetamide in DMF to afford 5-nitro-3,4-diphenyl-2-thiofuramide (**16**). Finally, the preparation of 5-nitro-3,4-diphenyl-2-furyl-thiazoles (**17a, b**) was achieved by reacting **16** with α-bromoketones.

Antimicrobial Activity

Table IV shows the *in vitro* antimicrobial properties of 5-nitro-3,4-diphenylfurans. Compounds which are described in this paper but are not listed in this table were found to be less active [minimal inhibitory concentrations (MIC)>30 μg/ml].

As listed in Table IV, most of the derivatives of amides **8** showed considerable inhibitory activity against *T. vaginalis*. Hydrazides **9**, **10** and hydrazones **11** were active not only against *T. vaginalis* but also against *S. aureus* and *M. tuberculosis*. However, most of the derivatives with a heterocyclic substituent at the 5 position of the furan ring did not show any antimicrobial activity.

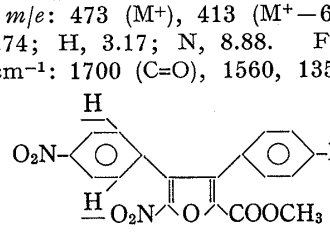
Experimental

Melting points are uncorrected. Instrumentation was as follows: IR, Jasco IR-E and IR-A; NMR, Varian A-60, JEOL PS-100; mass, Hitachi RMU-6E and RMU*7L; HPLC, Waters ALC/GPC-244. Spectral data were consistent with the assigned structures. Where analyses are indicated only by elemental symbols, analytical results obtained for these elements were within 0.3% of the theoretical values.

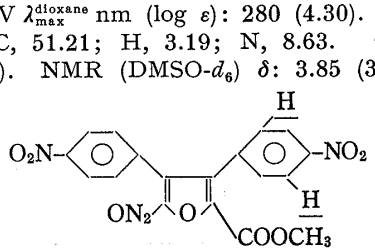
General Method of Nitration of Methyl 3,4-Diphenylfuran-2-carboxylate (1)——Method A: Acetyl nitrate [prepared from AC_2O (15.2 g) and f. HNO_3 (sp. gr. 1.50) (9.3 g) at 0°±5°] was stirred at the reaction temperature indicated in Table V and compound **1** (2.5 g, 0.009 mol) was added portionwise. Stirring was continued for a further 1.5 hr, then the reaction mixture was poured into ice-water. The crystals formed were filtered off, washed with water and dried under a vaccuum in the dark. The dry crystals were then washed with dry ether (20 ml) and the residues were recrystallized from acetone to afford compound **2**, mp 158—161° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1770, 1700 (C–O), 1560, 1305 (NO_2). NMR (DMSO-d_6) δ: 2.30 (3H, s, $-OCOCH_3$), 3.50 (3H, s, $-COOCH_3$), 7.20—7.40 (10H, m, phenyl protons), 7.70 (1H, s, dihydrofuran ring proton 5 pos.). MS *m/e*: 383 (M^+), 323 (M^+-60). UV $\lambda_{max}^{dioxane}$ nm (log ε): 264 (420). *Anal.* Calcd for $C_{20}H_{17}NO_7$: C, 62.60; H, 4.47; N, 3.65. Found: C, 62.20; H, 4.13; N, 3.72. The filtrates were combined and evaporated to dryness. The residue was packed onto a column (benzene–silica gel) for the separation of compound **3**, mp 171—173°. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O), 1560, 1350 (NO_2). NMR (DMSO-d_6) δ: 3.80 (s, 3H, CH_3), 7.20—7.48 (10H, m, phenyl protons). MS *m/e*: 323 (M^+). UV $\lambda_{max}^{dioxane}$ nm (log ε): 245 (4.40), 310 (4.15). *Anal.* Calcd for $C_{18}H_{13}NO_5$: C, 66.87; H, 4.05; N, 4.33. Found: C, 66.40; H, 3.88; N, 4.26. The yields shown in Table V were obtained by HPLC analysis of the dried reaction mixture.

Method B: To a suspension of **1** (2.5 g, 0.009 mol) in Ac_2O (12.5 ml) at the temperatures indicated in Table V, acetyl nitrate [prepared as in method A] was added dropwise. The mixture was stirred for 1.5 hr. Subsequent work-up was the same as in Method A.

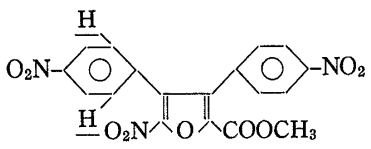
Method C: Following the procedure of method A, but with 4 drops of conc. H_2SO_4 added to the acetyl nitrate, compounds **4** and **5** were obtained. Compound **4**: mp 223—225° (dec.). IR ν_{max}^{KBr} cm^{-1} 1770, 1700 (C=O), 1560, 1350 (NO_2). NMR (DMSO-d_6) δ: 2.32 (3H, s, –OCOCH), 3.53 (3H, s, –COOCH), 7.50—7.70 (4H, m, nitrophenyl proton), 8.10—8.30 (3.5 H, m, nitrophenyl proton and dihydrofuran ring proton 5 pos.). MS *m/e*: 473 (M^+), 413 (M^+-60). UV $\lambda_{max}^{dioxane}$ nm (log ε): 280 (4.30). *Anal.* Calcd for $C_{20}H_{15}N_3O_{11}$: C, 50.74; H, 3.17; N, 8.88. Found: C, 51.21; H, 3.19; N, 8.63. Compound **5** mp 244—246°, IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O), 1560, 1350 (NO_2). NMR (DMSO-d_6) δ: 3.85 (3H, s, CH_3), 7.48 (2H, d, J=9.0 Hz,



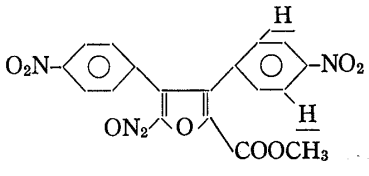
or



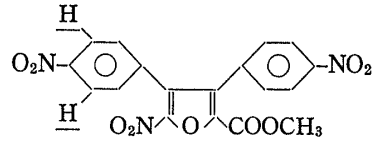
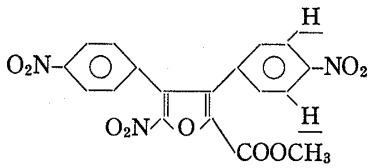
), 7.58 (2H, d, J=9.0 Hz,

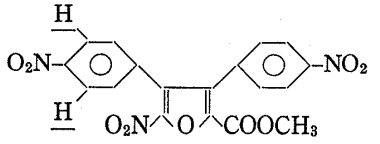
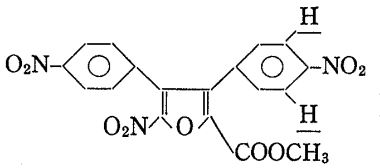


or



), 8.18 (2H, d, J=

9.0 Hz,  or ), 8.22 (2H, d, J=9.0 Hz,

 or ). MS m/e: 413 (M^+). UV $\lambda_{max}^{dioxane}$ nm ($\log \varepsilon$): 270 (4.60). *Anal.* Calcd for $C_{18}H_{11}N_3O_9$: C, 52.31; H, 2.68; N, 10.17. Found: C, 52.45; H, 2.40: N, 9.89. The yields determined by HPLC analysis are shown in Table V.

Method D: Following method B, but with 4 drops of conc. H_2SO_4 added to the acetyl nitrate, the results were as shown in Table V.

Conversion of 2 to 3——Method A: Compound **2** (1.0 g, 0.0026 mol) was suspended in pyridine (20 ml) and stirred at room temperature until it had completely dissolved. After standing for 12 hr, the solution was poured into ice-water. The crystals formed were filtered off and recrystallized from acetone–water to afford **3** (0.8 g, 85%), mp 171—173°, which was proved to be identical with a nitration product obtained by nitration method A.

Table V. Nitration of Compound **1**

Method	Reaction temp.(°C)	Yield (%) Compd. **2**[a]	Compd. **3**[a]	Total[a] (**2**+**3**)	Compd. **4**[b]	Compd. **5**[b]	Total[b] (**4**+**5**)
A	−40	24.4	12.1	36.5			
A	−30	24.5	12.2	36.7			
A	−20	23.1	11.0	34.1			
A	−20	23.1	11.0	34.1			
A	−10	20.3	10.2	30.5			
A	0	13.3	6.9	20.2			
A	+10	9.5	5.1	14.6			
A	+20	8.6	4.5	13.1			
B	−40	40.2	20.1	60.3			
B	−30	40.9	20.0	60.9			
B	−20	37.4	19.0	56.4			
B	−10	37.1	18.1	55.2			
B	0	36.8	18.4	55.2			
B	+10	23.4	12.1	35.5			
B	+20	18.4	10.2	28.6			
C	−40				30.4	10.2	40.6
C	−30				30.3	10.3	40.6
C	−20				22.7	7.8	30.5
C	−10				22.4	7.8	30.2
C	0				20.1	6.9	27.0
C	+10				17.4	6.1	23.5
C	+20				17.5	6.0	23.5
D	−40				30.4	10.1	40.5
D	−30				31.0	10.2	41.2
D	−20				22.9	7.7	30.6
D	−10				22.6	7.5	30.1
D	0				22.2	7.6	29.8
D	+10				18.9	6.5	25.4
D	+20				18.9	6.5	25.4

a) HPLC conditions: column; U-Porasil 30 cm×40 mm I.D., solvent; isooctane: ethylacetate: isopropanol=90: 10: 0.07, flow rate=2.0 m/min, detector; UV 245, 1.0 AUFS, chart speed; 0.2 inch/min, internal standard; phenol, R.T.; internal standard: 353, compound **2** : 1174, compound **3** : 436.

b) HPLC conditions: column; U-Porasil 30 cm×40 mm I.D., Solvent; isooctane: ethylacetate: isobutanol=75: 25: 0.2, flow rate; 2.0 ml/min, detector; UV 254, 1.0 AUFS, chart speed; 0.2 inch/min, internal standard; N-propyl parabene. R.T.; internal standard: 418, compound **4** : 1434, compound **5** : 873.

Method B. Compound **2** (1.0 g, 0.0026 mol) was dissolved in benzene and the solution was refluxed for 72 hr. After evaporation to dryness, the residue was recrystallized from acetone–water to give compound **3** (0.81 g, 87%), which was identical with the product obtained by the former method.

Conversion of 4 to 5——Method A: A suspension of **4** (1.0 g, 0.0021 mol) in pyridine (20 ml) was treated according to method A for removing acetic acid from **2** to afford **5** (0.70 g, 89%), mp 244—246°, which was proved to be identical with the compound obtained by nitration according to method C.

Method B: Compound **4** (1.0 g, 0.0021 mol) was treated according to method B for removing acetic acid from **2** to afford **5** (0.85 g, 87%), mp 244—246°, which was identical with the product obtained by method A.

5-Nitro-3,4-diphenyl-2-furoic Acid (6)——Compound **3** (8.0 g, 0.024 mol) was dissolved in dioxane (100 ml). The solution was stirred at room temperature and 2.5% NaOH (100 ml) was added dropwise until the reaction mixture became clear. The stirring was continued for a further 30 min, then the mixture was poured into ice-water, and acidified with 10% HCl. The crystals formed were filtered off and recrystallized from EtOH to give pale-yellow **6** (7.0 g, 92%), mp 259—260° (dec.). IR ν_{max}^{KBr} cm^{-1}: 3000—2500 (OH), 1710 (C=O). MS *m/e*: 309 (M^+), 265 (M^+-44). *Anal.* Calcd for $C_{17}H_{11}NO_5$: C, 66.02; H, 3.59; N, 4.53. Found: C, 66.32; H, 3.18; N, 4.20.

5-Nitro-3,4-diphenyl-2-furoyl Chloride (7)——A suspension of **6** (8.0 g, 0.026 mol) in thionyl chloride (40 ml) was refluxed for 3 hr. The yellowish crystalline residue obtained after distilling off the thionyl chloride was recrystallized from dry benzene–dry petroleum benzin to give **7** (7.0 g, 92%), mp 112—114°. IR ν_{max}^{KBr} cm^{-1}: 1765 (C=O). *Anal.* Calcd for $C_{17}H_{10}ClNO_4$: C, 62.30; H, 3.08; N, 4.27. Found: C, 62.51; H, 3.19; N, 4.50.

General Method for the Preparation of 5-Nitro-3,4-diphenyl-N-substituted 2-Furamides (8a—v)——To a solution of **7** (1.0 g, 0.003 mol) in dry ether, pyridine (3 drops) and an amine (0.006 mol) were added with stirring at room temperature. The mixture was stirred for 4—6 hr, then the crystals that had appeared were filtered off, washed with water, dried, and recrystallized from a suitable solvent to give **8a—v** (Table I).

3,3-Dimethyl-6-(5-nitro-3,4-diphenyl-2-furoylamino)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid (8w)——A solution of 6-aminopenicillanic acid (0.4 g, 0.002 mol) in acetone was treated with 25% $NaHCO_3$ (20 ml) and the mixture was cooled to 0—5°. A solution of **7** (0.6 g, 0.0018 mol) in acetone (20 ml) was then added dropwise and the whole was stirred at room temperature for 4 hr. The acetone was removed under reduced pressure. The residual liquid was then washed with ether. The aqueous layer was acidified to pH 2.0 with 10% HCl and extracted with EtOAc. The extract was washed with H_2O, dried and evaporated to dryness. The residue was recrystallized from acetone to afford **8w** (Table I).

5-Nitro-3,4-diphenyl-2-furoylhydrazine (9) and N,N′-Bis[5-nitro-3,4-diphenyl-2-furoyl]hydrazine (10h)——Hydrazine hydrate (1.5 g, 0.03 mol) was dissolved in EtOH (10 ml) and the solution was cooled to 0—3°. Compound **7** (1 g, 0.003 mol) in benzene (20 ml) was added dropwise with stirring, and the stirring was continued for a further 15 min. AcOH was added to neutralize excess hydrazine. The reaction mixture was evaporated to dryness, and the residue was washed with H_2O, then fractionally recrystallized from benzene to give **9** (0.6 g, 60%). mp 169—170° (dec.). IR ν_{max}^{KBr} cm^{-1}: 2850—3300 (NH), 1665 (C=O). MS *m/e*: 323 (M^+). *Anal.* Calcd for $C_{17}H_{13}N_3O_4$: C, 63.15; H, 4.05; N, 13.00. Found: C, 63.31; H, 3.79, N, 12.92 and **10h** (0.2 g, 20%) mp 248—249° (dec.) (Table III).

Acetone 5-Nitro-3,4-diphenyl-2-furoylhydrazone (11a)——Compound **9** (1.0 g, 0.003 mol) was dissolved in acetone (50 ml) and the solution was refluxed for 2 hr. The solution was concentrated, then cooled. The crystals which formed on cooling were collected by filtration and recrystallized from acetone to afford **11a** (0.8 g, 72%) (Table II).

Aldehyde 5-Nitro-3,4-diphenyl-2-furoylhydrazones (11b—e)——An aldehyde (0.03 mol) and acetic acid (2 drops) were added to a solution of **9** (1.0 g, 0.03 mol) in EtOH (20 ml). The mixture was refluxed for 1 hr, then cooled. The crystals which separated were filtered off and recrystallized to give **11b—e** (Table II).

N-(5-Nitro-3,4-diphenyl-2-furoyl)-N′-acylhydrazines (10a—h)——A solution of **7** (1.0 g, 0.003 mol) in ether was cooled to 0—5°. An acylhydrazide (0.003 mol) in pyridine was added dropwise at room temperature with stirring, which was continued for 3—8 hr. After the reaction, the crystals which had formed were collected by filtration and recrystallized to give **10a—h** (Table III).

2-Substituted-5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazole (12a—h)——A suspension of **10a—h** (0.003 mol) in $POCl_3$ (10 ml) was refluxed for 3—8 hr. The reaction mixture was evaporated to dryness to leave a residue, to which ice-water was added. The solid which formed was filtered off and recrystallized to give **12a—h** (Table III).

2-Amino-5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazole (12i)——A suspension of **9** (1.0 g, 0.003 mol) in MeOH (40 ml) was treated with cyanogen bromide (0.4 g, 0.0031 mol) and refluxed for 1.5 hr, then allowed to cool. The crystals that separated were filtered off and recrystallized from EtOH to give **12i** (Table III).

2-[Bis(hydroxymethyl)amino]-5-(5-nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazole (12j)——Compound **12i** (1.2 g, 0.005 mol) and formalin (37%) (2.8 g) were dissolved in DMF and heated on a steam bath for 30 min. The reaction mixture was then poured into ice-water. The solid which formed was filtered off and recrystallized to give **12j** (Table III).

5-(5-Nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazol-2-one (13)——A solution of **9** (1 g, 0.003 mol) in 100 ml

of toluene was stirred and warmed on steam bath while phosgene was introduced beneath the surface of liquid. After 1 hr, the mixture was evaporated to dryness. The residue was recrystallized from methanol to afford **13** (0.5 g, 52%), mp 200—201° (dec.). MS *m/e*: 349 (M^+). *Anal.* Calcd for $C_{18}H_{11}N_3O_5$: C, 61.89; H, 3.17; N, 12.03. Found: C, 61.71; H, 3.00, N, 11.95.

5-(5-Nitro-3,4-diphenyl-2-furyl)-1,3,4-oxadiazole-2-thione (14)——Compound **9** (1.0 g, 0.003 mol) was dissolved in dioxane (20 ml) and thiophosgene (0.5 g, 0.003 mol) was added at room temperature. The mixture was stirred at 50° for 12 hr and then poured into ice-water. The solid which separated was recrystallized from EtOH to give **14** (0.4 g, 32%), mp 165—166° (dec.). MS *m/e*: 365 (M^+). *Anal.* Calcd for $C_{18}H_{11}N_3O_4S$: C, 59.17; H, 3.03; N, 11.50. Found: C, 59.30; H, 3.29; N, 11.70.

5-Nitro-3,4-diphenyl-2-furonitrile (15)——A suspension of **8a** (1.0 g, 0.003 mol) in $POCl_3$ (20 ml) was refluxed for 3 hr, then evaporated to dryness. Ice-water was poured onto the residue. The solid that separated was filtered off and recrystallized from EtOH to give **15** (0.6 g, 68%), mp 142—144°. IR ν_{max}^{KBr} cm^{-1}: 2240 (C≡N). MS *m/e*: 290 (M^+). *Anal.* Calcd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.56; H, 3.01; N, 9.98.

5-Nitro-3,4-diphenyl-2-thiofuramide (16)——Thioacetamide (0.45 g, 0.006 mol) and **15** (1.0 g, 0.003 mol) were dissolved in DMF (10 ml) which was saturated with anhydrous HCl and heated on steam bath for 30 min. The mixture was then cooled with ice-water after being concentrated to about 5 ml. The crystals that formed were recrystallized from EtOH to afford **16** (0.3 g, 25%) mp 180—182° (dec.). IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1300 (C=S). MS *m/e*: 324 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.96; H, 3.70; N, 8.60. Found: C, 62.89; H, 3.55; N, 8.53.

5-Methyl-2-(5-nitro-3,4-diphenyl-2-furyl)thiazole (17a)——Compound **16** (0.8 g, 0.002 mol) and chloroacetone (0.2 g, 0.02 mol) were dissolved in EtOH (100 ml). The solution was refluxed for 24 hr, then cooled. The product that separated was recrystallized from dioxane–EtOH to give **17a** (0.3 g, 25%), mp 172—174°. MS *m/e*: 362 (M^+). *Anal.* Calcd for $C_{20}H_{14}N_2O_3S$: C, 66.29; H, 3.90; N, 7.73. Found: C, 66.51; H, 3.69; N, 7.95.

2-(5-Nitro-3,4-diphenyl-2-furyl)-5-phenylthiazole (17b)——Compound **16** (0.8 g, 0.002 mol) and chloroacetophenone (0.3 g, 0.002 mol) were dissolved in EtOH (100 ml). The solution was refluxed for 24 hr, then cooled. The solid that separated was recrystallized from dioxane–EtOH to afford for **17b** (0.6 g, 50%), mp 195—197°. MS *m/e*: 424 (M^+). *Anal.* Calcd for $C_{25}H_{16}N_2O_3S$: C, 70.74; H, 3.80; N, 6.60. Found: C, 70.56; H, 4.00, N, 6.41.

References and Notes

1) K. Yamamoto and S. Yoshina, *Yakugaku Zasshi*, **95**, 1218 (1975).
2) *a*) S. Yoshina and K. Yamamoto, *Yakugaku Zasshi*, **95**, 219 (1975); *b*) *Idem*, *ibid.*, **95**, 741 (1975).
3) H. Saikachi, R. Kimura, and H. Hoshida, *Yakugaku Zasshi*, **73**, 1132 (1953).
4) T. Sasaki, *Chem. Pharm. Bull.*, **2**, 95 (1954).
5) W.R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).
6) I. Saikawa, *Yakugaku Zasshi*, **84**, 212 (1964).
7) W.R. Sherman and A.V. Esch, *J. Med. Chem.*, **8**, 25 (1965).