Halomethyl-1,2,4-Oxadiazoles. I. Reactions Employing 5-Chloromethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole

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Received August 17, 1971

Since the work of Dodd and Stillman in 1944 (1), 5-nitrofurans have been recognized as potent antibacterial agents. We were interested in exploring the potential of 3-(5-nitro-2-furyl)-1,2,4-oxadiazoles as antibacterial agents. Previously, Eloy and Lenaers had prepared several 3-(5-nitro-2-furyl)-1,2,4-oxadiazoles utilizing the classical procedure of Tiemann (2). They had also prepared this type compound by the reaction of a nitrile with a nitrile oxide and by the reaction of a nitrile with a hydroxamyl chloride (3).

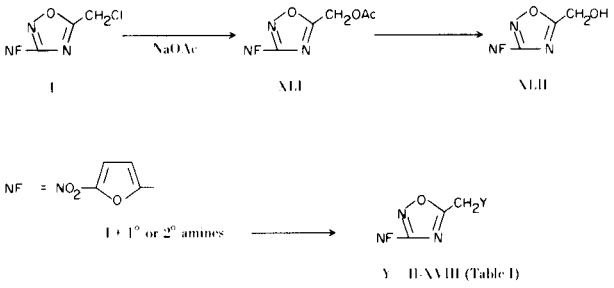
Pallazo and co-workers have reported on the nucleophilic displacement of halogen in 5-halomethyl-1,2,4-oxadiazoles by various amines (4). Their study included phenyl, substituted phenyl, benzyl, pyridyl, naphthyl, and 1-tetrahydronaphthyl derivatives. These compounds were of interest as antiinflammatory and as antitussive agents.

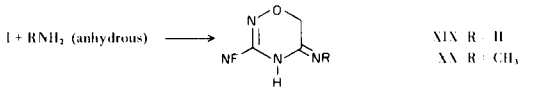
We have studied the displacement of the halogen in 5-chloromethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (I) (5). Primary, secondary, and cyclic amines, when refluxed with compound I, yielded, in most cases, the expected oxadiazoles (II-XVIII). *N,N*-dimethylformamide was found to aid this displacement and, therefore, was used throughout this series of reactions. Products obtained as oils were converted to the hydrochloride salt for purification, analysis, and antibacterial screening. The chemical data on these compounds are summarized in Table I.

Surprisingly, compound I, when treated with liquid ammonia or anhydrous methylamine, did not give the respective products XXXVIII and XXXIX. In the reaction with liquid ammonia a yellow solid (dec. 220-222°) was isolated (6). Although the elemental analysis was consistent for that expected for compound XXXVIII (free base), chemical reactivities, solubilities, ir and nmr, were not consistent. The latter studies and independent synthesis led to the identification of the product as 5-amino-3-(5-nitro-2-furyl)-6*H*-1,2,4-oxadiazine (XIX).

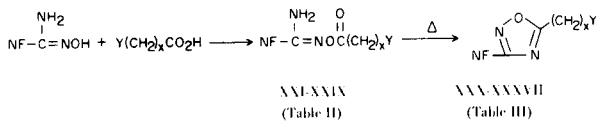
With anhydrous methylamine the reaction did not proceed as well as with ammonia but the product was the methyl analog XX. The scope of the reaction was extended to other halo substituted side chains and also to the thiophene analog of XIX. Discussion of this work will be reported in a later publication.

SCHEME 1





SCHEME 2

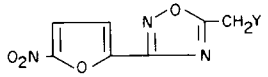


Two methods were devised to obtain the desired 5-aminomethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole. The first method involved the Delepine reaction. Compound I was reacted with hexamine in chloroform to form the iminium salt which underwent acid hydrolysis to the amine salt (XXXVIII).

The second method is shown in Scheme 2. The mixed anhydride of aceturic acid was formed and reacted with 5-nitro-2-furamidoxime (5) to yield the *O*-acylated amidoxime (XXI) which was ring closed on heating to *N*-[(3-(5-nitro-2-furyl)-1,2,4-oxadiaz-5-yl)methyl]acetamide

TABLE I

3-(5-Nitro-2-furyl)-5-methylamino-1,2,4-oxadiazoles



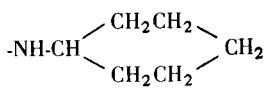
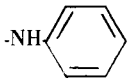
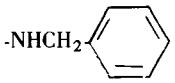
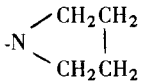
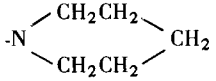
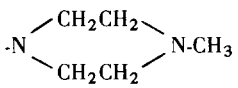
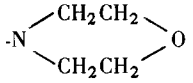
	Y	M.p., °C	Recryst. from	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
II	$-NHCH_2CH_3$	215-220 dec.	(a)	5	$C_9H_{10}N_4O_4 \cdot HCl$	39.37	4.04	20.40	39.12	4.09	20.32
III	$-NH(CH_2)_2CH$	215-219 dec.	(b)	13	$C_{10}H_{12}N_4O_4 \cdot HCl$	41.61	4.54	19.41	41.50	4.68	19.41
IV	$-NH(CH_2)_2OH$	114-116	(a)	42	$C_9H_{10}N_4O_5$	42.52	3.97	22.04	42.48	3.95	21.98
V	$-N(CH_3)_2$	210-215	(a)	87	$C_9H_{10}N_4O_4 \cdot HCl$	39.37	4.04	20.40	39.17	4.19	20.42
VI	$-N(CH_2CH_3)_2$	195-196	(a)	31	$C_{11}H_{14}N_4O_4 \cdot HCl$	43.64	4.99	18.51	43.55	5.21	18.32
VII	$-N((CH_2)_2OH)_2$	128-130	(a)	50	$C_{11}H_{14}N_4O_6$	44.30	4.73	18.78	44.31	4.94	18.58
VIII	$-N((CH_2)_2CH_3)_2$	162-164	(b)	30	$C_{13}H_{18}N_4O_4 \cdot HCl$	47.21	5.79	16.94	47.52	6.08	16.80
IX	$-N((CH_2)_3CH_3)_2$	128-129	(c)	56	$C_{15}H_{22}N_4O_4 \cdot HCl$	50.21	6.46	15.61	50.18	6.53	15.61
X	$-NHC(CH_3)_3$	244-245	(a)	25	$C_{11}H_{14}N_4O_4 \cdot HCl$	43.64	4.99	18.51	43.74	4.80	18.73
XI	$-NHC(CH_2OH)_3$	126-128	(a)	40	$C_{11}H_{14}N_4O_7$	42.04	4.49	17.83	42.28	4.50	17.66
XII		200-204	(a)	61	$C_{13}H_{16}N_4O_4 \cdot HCl$	47.49	5.21	17.04	47.53	5.48	16.93

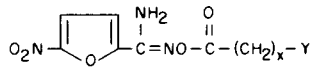
TABLE I (continued)

	Y	M.p., °C	Recryst. from	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIII		140-141	(a)	49	$C_{13}H_{10}N_4O_4 \cdot HCl$	48.38	3.44	17.36	50.14	3.29	17.21
XIV		85-88	(a)	33	$C_{14}H_{12}N_4O_4$	56.00	4.03	18.66	56.04	4.05	18.81
XV		195 dec.	(a)	75	$C_{11}H_{12}N_4O_4 \cdot HCl$	43.94	4.36	18.63	44.19	4.45	18.57
XVI		81-82	(a)	66	$C_{12}H_{14}N_4O_4$	51.79	5.07	20.14	51.85	5.30	19.95
XVII		210-215 dec.	(a)	46	$C_{12}H_{15}N_5O_4 \cdot HCl$	43.71	4.89	21.24	44.00	5.09	21.09
XVIII		125-126	(a)	68	$C_{11}H_{12}N_4O_5$	47.14	4.32	19.99	47.19	4.42	20.09

(a) Ethanol, (b) 2-propanol, (c) ethyl acetate.

TABLE II

O-Acyl-(5-Nitro-2-furyl)amidoximes

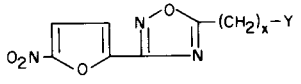


	Y	X	M.p., °C	Method	Recryst. from	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXI	-NHCCH$_3$	1	196-198 dec.	Mixed anhydride	(d)	48	$C_9H_{10}N_4O_6$	40.00	3.73	20.74	39.87	3.73	20.84
XXII	-N(CH$_3$)CCH$_3$	1	167-168	D.C.C.	(b)	61	$C_{10}H_{12}N_4O_6$	42.25	4.26	19.71	42.04	4.34	19.92
XXIII	-NHCCH$_3$	2	175-176 dec.	Mixed anhydride	(d)	41	$C_{10}H_{12}N_4O_6$	42.25	4.26	19.71	42.04	4.36	19.71
XXIV	-NHCCH$_3$	3	143-145 dec.	Mixed anhydride	(e)	31	$C_{11}H_{14}N_4O_6$	44.29	4.74	18.78	44.15	4.73	18.97
XXV	-NHCCH$_3$	5	141-143 dec.	Mixed anhydride	(c)	37	$C_{13}H_{18}N_4O_6$	47.85	5.56	17.17	47.65	5.55	17.39
XXVI	-NHCCH$_2$Cl	1	167-169 dec.	D.C.C.	(a)	19	$C_9H_9ClN_4O_6$	35.48	2.97	18.39	35.48	2.98	18.20
XXVII	-NHCCH$_2$CH$_3$	1	172-173 dec.	D.C.C.	(e)	46	$C_{10}H_{12}N_4O_6$	42.25	4.26	19.71	41.92	4.29	19.60
XXVIII	-NHC(C$_6$H$_5$)	1	183-184 dec.	Mixed anhydride	(e)	70	$C_{14}H_{12}N_4O_6$	50.60	3.64	16.86	50.46	3.89	16.89
XXIX	-SCCH$_3$	1	162-163	D.C.C.	(a)	57	$C_9H_9N_3O_6S$	37.63	3.16	14.63	37.36	3.12	14.56

(a) Ethanol, (b) 2-propanol, (c) ethyl acetate, (d) nitromethane, (e) acetonitrile.

TABLE III

3-(5-Nitro-2-furyl)-5-alkylamino-1,2,4-oxadiazoles



	Y	X	M.p., °C	Recryst. from	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXX	-NHCCH$_3$	1	156-158	(a)	68	$C_9H_8N_4O_5$	42.86	3.20	22.21	43.03	3.08	21.98
XXXI	-N(CH$_3$)-CCH$_3$	1	148-150	(b)	79	$C_{10}H_{10}N_4O_5$	45.11	3.79	21.05	45.25	3.95	21.17
XXXII	-NH-CCH$_3$	2	156-158	(b)	49	$C_{10}H_{10}N_4O_5$	45.11	3.79	21.05	45.10	3.99	21.04
XXXIII	-NHCCH$_3$	3	132-133	(b)	41	$C_{11}H_{12}N_4O_5$	47.14	4.32	19.99	46.80	4.63	19.81
XXXIV	-NHCCH$_3$	5	96-98	(a)	67	$C_{13}H_{16}N_4O_5$	50.64	5.23	18.17	50.73	5.46	18.22
XXXV	-NHCCH$_2$Cl	1	113-115	(b)	56	$C_9H_7ClN_4O_5$	37.71	2.46	19.55	37.77	2.77	19.70
XXXVI	-NHCCH$_2$CH$_3$	1	138-140	(a)	91	$C_{10}H_{10}N_4O_5$	45.11	3.79	21.05	45.15	3.85	20.98
XXXVII	-NHC-C$_6$H$_5$	1	183-185	(e)	69	$C_{14}H_{10}N_4O_5$	53.51	3.21	17.83	53.23	3.15	18.01

(a) Ethanol, (b) 2-propanol, (c) ethyl acetate, (d) nitromethane, (e) acetonitrile.

TABLE IV

In Vitro Activity of Selected Compounds

Compound	*Aerobacter aerogenes* ATCC 13048	*Pseudomonas aeruginosa* ATCC 10145	*Proteus mirabilis* Finland 9	*E. coli* Juhl	*E. coli* ATCC 1175	*Salmonella typhimurium* Ed. 9	*Staph aureus* 209 P	*Staph aureus* Smith
XXI	50	>200	>200	25	25	12.5	50	50
XXII	50	>200	200	25	25	12.5	50	50
XXV	200	>200	>200	200	100	100	50	50
XXVI	50	>200	200	12.5	12.5	6.2	25	25
XXVII	50	>200	200	25	12.5	12.5	50	50
XXX	200	>200	200	50	25	50	50	50
XXXII	>200	>200	>200	25	25	50	50	25
XXXV	100	>200	200	25	12.5	25	12.5	6.2
XXXVI	>200	>200	>200	50	25	50	50	25
XXXVIII	50	>200	100	12.5	12.5	12.5	50	50
XXXIX	50	>200	200	25	12.5	25	50	50
XL	>200	>200	>200	>200	200	>200	25	25
XLII	50	>200	100	12.5	12.5	12.5	50	25
XLIV	200	>200	200	100	50	100	12.5	12.5

Values represent parts per million required to completely inhibit growth in a broth dilution test at 24 hours. Appropriate amounts of the compound in diluent (dissolved in dimethylformamide and water) are added at 2-fold dilution levels to 5 ml. of BHI broth (Difco). Twenty-four hour cultures in BHI broth are diluted 1:100 in sterile water, and 0.1 ml. of the diluted culture is used as the inoculum for each tube. The tubes are incubated at 37°, and the presence or absence of growth in the tubes is recorded at 24 hours.

(XXX). This compound was then hydrolyzed to the desired aminomethyl compound (XXXVIII). The synthesis of 5-methylamino-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (XXXIX) was accomplished through a similar acylation of the amidoxime, ring closure, and acid hydrolysis.

Several additional amides of compound XXXVIII also were formed using the same method. Compounds XXII, XXVI, XXVII, and XXIX were prepared by a modification employing dicyclohexylcarbodiimide as the condensing agent forming the *O*-acylated amidoximes. Using these preferred methods (acid chloride acylation was not fruitful), the chain length at position 5 of the oxadiazole ring could be varied by the acylation of the amidoxime with the appropriate acid followed by ring closure.

Table II shows the *O*-acylated derivatives of 5-nitro-2-furamidoxime, and Table III the respective amides formed on heating. 5-Acetylmercaptomethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (XL) was prepared in essentially the same way.

In addition to the various amines, the halogen in I was also displaced by acetate to yield compound XLI, which upon acid hydrolysis, was converted to the hydroxymethyl compound (XLII). The presence of the 5-nitrofuryl group did not permit an alkaline hydrolysis as Angelini (7) has used in a similar reaction to obtain 5-hydroxymethyl-3-phenyl-1,2,4-oxadiazole.

Jaunin has also reported several displacement reactions on 5-chloromethyl-3-phenyl-1,2,4-oxadiazole using dimethylsulfoxide as solvent and potassium carbonate as acid acceptor (8). The nitrofuran moiety is unstable in the presence of potassium carbonate in dimethylsulfoxide. However, the displacement of the chloro group in I was effected successfully with phenol (XLIII), thiourea (XLIV) and potassium thiocyanate (XLV) using acetone or ethanol as solvents. The anomolous reactions reported by Jaunin in the cases of sodium cyanide, *p*-nitrobenzaldehyde, and transolefins led only to decomposition with the 5-nitrofuran analog (I).

Several compounds described have good antibacterial activity *in vitro*, as shown in Table IV. The spectrum is typical of a nitrofuran with activity of less than 100 ppm against *Staphylococcus aureus*, *Salmonella typhimurium* and *Escherichia coli*.

Compound XXX displayed the greatest *in vivo* activity in the mouse protection test (9). The CD_{50} for *Staphlococcus aureus* Smith was 55 mg./kg. by oral route of administration; for *Salmonella typhimirium*, 660 mg./kg. (oral administration); and *E. coli*, 110-220 mg./kg. orally.

EXPERIMENTAL

All melting points are uncorrected. Analyses were performed by Orville Kolsto and associates of Abbott Laboratories.

General Method for Compounds II-XVIII.

To 100 ml. of refluxing benzene containing 5 ml. of *N,N*-dimethylformamide was added 4.6 g. (0.02 *M*) of 5-chloromethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (I), and two equivalents of the amine. Refluxing was continued for twelve hours. The benzene solution was cooled, and the hydrochloride of the amine starting material was filtered. The filtrate was concentrated to an oil and cooled in an ice bath. In some cases, crystallization occurred. In these cases, the compound was recrystallized from an appropriate solvent for analysis.

If the oil did not crystallize, it was dissolved in 20 ml. of ether, and the hydrochloride salt prepared by adding ethereal hydrogen chloride. In general, the hydrochloride salts were purified by recrystallization from ethanol.

Mixed Anhydride Method for *O*-Acyl-5-nitro-2-furamidoximes.

Several acids: aceturic acid, *N*-acetyl-β-alanine, 4-acetamidobutyric acid, 6-acetamidohexanoic acid, and hippuric acid were combined with 5-nitro-2-furamidoxime by the mixed anhydride method described below.

Equimolar amounts of the appropriate acylated aminoacid and triethyl amine were dissolved in dry acetone (10 g./100 ml.). The resulting solution was cooled and stirred with adequate precautions to insure anhydrous conditions. An equivalent of ethyl chloroformate dissolved in acetone was added dropwise, and stirred for four hours.

The triethylamine hydrochloride was filtered. The filtrate was added dropwise with stirring to an acetone solution containing an equivalent of 5-nitro-2-furamidoxime (12 g./100 ml.). After the addition was completed, the solution was heated at 40° for 12 hours, and then cooled. The product crystallized from solution, was filtered and then recrystallized from an appropriate solvent.

Carbodiimide Method for *O*-Acyl-5-nitro-2-furamidoximes.

Several acids: *N*-chloroacetylglycine, *N*-acetylsarcosine (10), *N*-proprionylglycine (11) and acetylmercaptoacetic acid formed *O*-acyl derivatives of 5-nitro-2-furamidoxime through the use of *N,N*-dicyclohexylcarbodiimide by the general method described below.

One equivalent of 5-nitro-2-furamidoxime was dissolved in anhydrous acetone (1 g./25 ml.) containing an equivalent of *N,N*-dicyclohexylcarbodiimide. The solution was stirred, taking suitable precautions to preserve anhydrous conditions. An equimolar quantity of acid dissolved in acetone or acetonitrile was added dropwise and allowed to stir overnight at room temperature. The urea was filtered, and the filtrate was concentrated to dryness. The product was crystallized from a suitable solvent.

General Method for Ring Closure of *O*-Acyl-5-nitro-2-furamidoximes.

The *O*-acyl-5-nitro-2-furamidoxime was placed in a round bottom flask and heated by means of an oil bath to its melting point and held for 10 minutes or until rapid bubbling ceased. The melt was poured rapidly into a crystallizing dish. Upon cooling, the oil solidified and was broken into small pieces. It was recrystallized from an appropriate solvent.

5-Aminomethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole Hydrochloride (XXXVIII).

Method I.

Compound I (9.2 g., 0.02 *M*) and 5.6 g. (0.04 *M*) of hexamethylene tetramine were refluxed in 50 ml. of chloroform for 2 hours. The white quaternary salt was filtered and suspended

in 50 ml. of ethanol containing 15 ml. of concentrated hydrochloric acid. The mixture was allowed to stand at room temperature for 48 hours, then neutralized with sodium carbonate, and extracted three times with ether. The extracts were combined and dried over magnesium sulfate. Ethereal hydrogen chloride was added dropwise until the solution was highly acidic. The white salt precipitated, m.p. 194-195° dec., yield, 1.0 g. This compound was identical in all respects (m.p., ir, nmr) to the compound prepared by Method 2.

Method 2.

Five g. of compound XXX were refluxed in 25 ml. of 2 *N* hydrochloric acid for 1 hour. The solution was concentrated to give the hydrochloride salt of the product. The salt was recrystallized from boiling propanol, yield 2.9 g. (59%), m.p. 194-195°.

Anal. Calcd. for $C_7H_6N_4O_4$·HCl: C, 34.09; H, 2.86; N, 22.73. Found: C, 33.90; H, 3.12; N, 22.71.

Neutralization of the hydrochloride salt with an equivalent amount of sodium bicarbonate gave the free base, m.p. 88-89°.

5-Methylaminomethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (XXXIX).

Compound XXXI (10.5 g., 0.0039 *M*) was refluxed for 2 hours in 120 ml. of 2 *N* hydrochloric acid and then concentrated to dryness, yielding the hydrochloride salt of the product. The product was recrystallized from boiling ethanol, m.p. 202-204° dec., yield 6.6 g. (65%).

Anal. Calcd. for $C_8H_8N_4O_4$·HCl: C, 36.86; H, 3.48; N, 21.50. Found: C, 36.71; H, 3.36; N, 21.55. The free base melted at 58-59°.

5-Acetylmercaptomethyl-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (XL).

Ten g. of *O*-acetylmercaptoacetyl-5-nitro-2-furamidoxime (XXIX) was heated to 170° by means of an oil bath and held at this temperature for 10 minutes. The melt was cooled and solidification occurred. The solid was recrystallized from 400 ml. of boiling propanol, m.p. 113-115°, weight, 6.5 g. (46%).

Anal. Calcd. for $C_9H_7N_3O_5S$: C, 40.14; H, 2.62; N, 15.61. Found: C, 40.17; H, 2.72; N, 15.69.

3-(5-Nitro-2-furyl)-1,2,4-oxadiazole-5-methanol (XLII).

A mixture containing 5.0 g. (0.022 *M*) of I, 1.8 g. of anhydrous sodium acetate (0.022 *M*), 60 ml. of absolute ethanol, and 2 ml. of dimethylformamide was heated at reflux for 24 hours. The reaction mixture was filtered and the filtrate taken to dryness. The ether extract was washed with water, treated with charcoal, and the resulting yellow solution was dried over magnesium sulfate. After filtering, the ether solution was concentrated to dryness under vacuo. The oily residue was the crude acetoxy derivative (XLI) as shown by ir analysis (Carbonyl = 1760 cm^{-1}).

The crude oil was taken into solution with 50 ml. of 95% ethanol, and 10 ml. of concentrated hydrochloric acid was added. The mixture was refluxed for 8 hours and then concentrated under vacuum. The resulting solid was crystallized from boiling ethanol yielding 2.5 g. of a white solid (XLII), m.p. 132-134°.

Anal. Calcd. for $C_7H_5N_3O_5$: C, 39.82; H, 2.39; N, 19.90. Found: C, 40.09; H, 2.35; N, 19.76.

3-(5-Nitro-2-furyl)-5-phenoxymethyl-1,2,4-oxadiazole (XLIII).

Compound I (4.6 g.) was stirred in anhydrous acetone at room temperature while 2.0 g. of phenol, a crystal of sodium iodide, and 1.4 g. of potassium carbonate were added. Stirring was continued for 20 hours. The solution was filtered and concentrated to a brown oil. Upon addition of ethanol, the oil crystallized. The solid was then recrystallized from boiling ethanol. The yield was poor, 0.4 g., 14%, m.p. 139-141° dec.

Anal. Calcd. for $C_{13}H_9N_3O_5$: C, 54.36; H, 3.16; N, 14.63. Found: C, 54.43; H, 3.38; N, 14.51.

2-[(3-(5-Nitro-2-furyl)-1,2,4-oxadiazole-5-yl)methyl]-2-thiopseudourea Hydrochloride (XLIV).

Compound I (4.6 g., 0.02 *M*) and 1.52 g. of (0.02 *M*) of thiourea were refluxed in 60 ml. of absolute ethanol for 4 hours. During the refluxing, solid began to crystallize from the reaction mixture. The solution was cooled using an ice bath. The solid was collected by filtration, yielding 4.0 g. of the white thiouronium salt. The compound was recrystallized from boiling ethanol, m.p. 190° dec.

Anal. Calcd. for $C_8H_7N_5O_4S$·HCl: C, 31.43; H, 2.64; N, 22.91. Found: C, 31.58; H, 2.65; N, 22.71.

Thiocyanic Acid, [3-(5-Nitro-2-furyl)-1,2,4-oxadiazol-5-yl]methyl Ester (XLV).

The reaction was run in the same manner as above, substituting potassium thiocyanate for thiourea, yield 3.8 g., 76%, m.p. 90-94°.

Anal. Calcd. for $C_8H_4N_4O_4S$: C, 38.10; H, 1.60; N, 22.21. Found: C, 37.91; H, 1.71; N, 22.16.

Acknowledgment.

The authors are grateful to Mr. Robert Bower, Mr. Don Kenney and Mrs. Charlene Vojtko for microbiological data, to Mr. Allan Kammer for infrared spectra, and to Dr. Richard Mattoon for nuclear magnetic resonance spectra.

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