(3:97) to get the octa-O-benzyl-sucrose (XIV) (6.05 g.), $[\alpha]_D^{20}$ +38.6° (c=1.62, $CHCl_3$): lit. $[\alpha]_D^{26}$ +31.6° (c=1.65, $CHCl_3$).[5] *Anal.* Calcd. for $C_{68}H_{70}O_{11}$: C, 76.81; H, 6.63. Found: C, 77.11; H, 6.79.

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Jun-ichi Matsumoto and Shinsaku Minami*1 : Studies on Nitrofuran Derivatives. Ⅷ.*2 Synthesis of 3-(5-Nitro-2-furyl)isoxazoles.

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In our previous paper,*2 the synthesis of 3-(5-nitro-2-furyl)-Δ^2-isoxazolines and -isoxazoles which involved the 1,3-dipolar cycloaddition reactions of 5-nitro-2-furonitrile oxide (Ⅴ) with various enamines was reported. The excellent antibacterial activities of these nitrofuran derivatives prompted us further study on the synthesis of this class of the compounds. The present paper deals with the synthesis from 5-nitro-2-furhydroxamoyl chloride[1] (Ⅰ) and compounds containing active methylene groups.

As one of the methods for the preparation of isoxazoles, Quilico[2] has studied a reaction of hydroxamoyl chlorides with active methylene compounds. Application of this reaction to the hydroxamoyl chloride (Ⅰ) using β-keto esters, β-diketones and β-keto nitriles led to the formation of a series of 4,5-di-substituted 3-(5-nitro-2-furyl)isoxazoles (Ⅳ). The reaction was carried out effectively by mixing equimolar amounts of the hydroxamoyl chloride (Ⅰ) and the sodium salt (Ⅱ or Ⅲ) of the active methylene compound at low temperature.

The hydroxamoyl chloride (Ⅰ) reacted readily with sodioacetoacetates and sodiobenzoylacetate to give 5-methyl-3-(5-nitro-2-furyl)-4-isoxazolecarboxylates (Ⅳa and Ⅳb) and ethyl

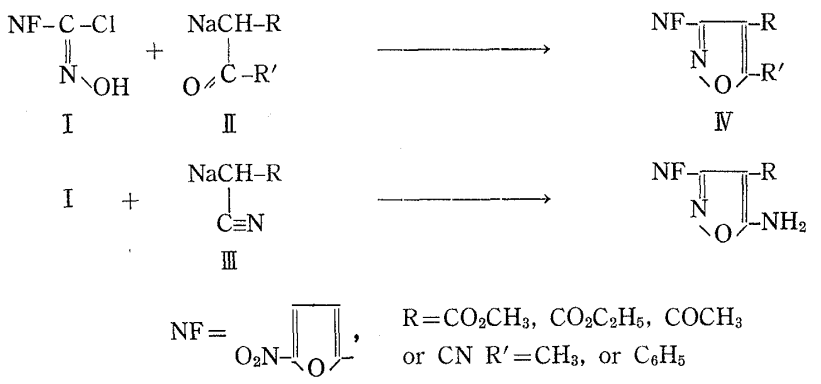

Chart 1.

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*2 Part Ⅶ: This Bulletin, **15**, 366 (1967).

1) R. Lenaers, F. Eloy: Helv. Chim. Acta, **46**, 1067 (1963).

2) A. Quilico: "The Chemistry of Heterocyclic Compounds" A. Weissberger Ed., 19 (1962), John Wiley & Sons, Inc., New York, and references cited therein.

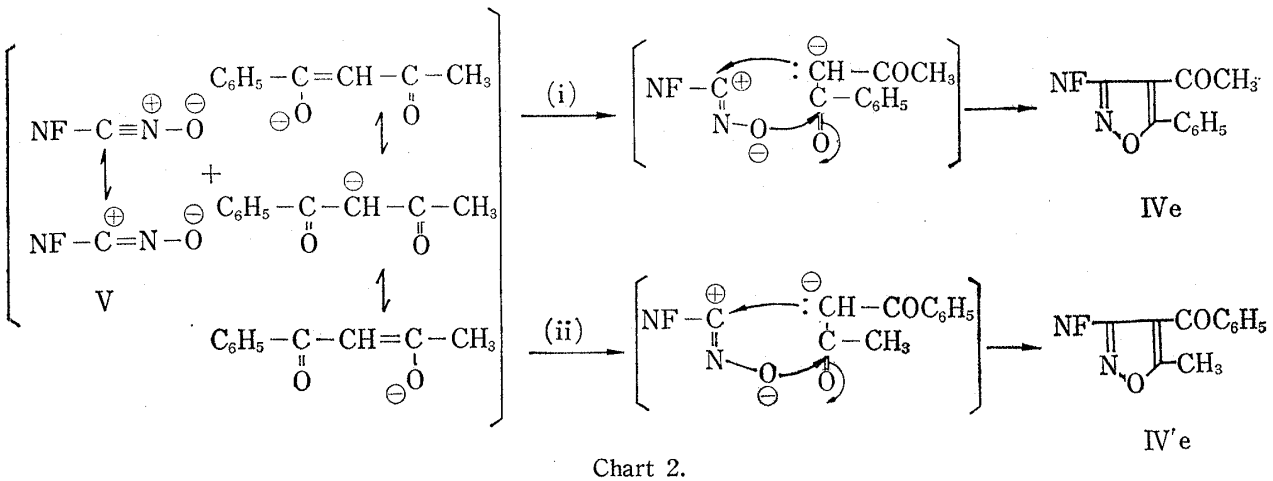


Chart 2.

5-phenyl-3-(5-nitro-2-furyl)-4-isoxazolecarboxylate (Ⅳc), respectively. With sodioacetylacetone, the hydroxamoyl chloride (I) afforded 4-acetyl-5-methyl-3-(5-nitro-2-furyl)isoxazole (Ⅳd).

The reaction with sodiobenzoylacetone produced an isoxazolyl ketone as a sole product which showed an absorption band at 1655 cm^{-1} in its infrared spectrum (KBr). In this case either of the two structures, 4-acetyl-5-phenyl (Ⅳe) and 4-benzoyl-5-methyl-3-(5-nitro-2-furyl)isoxazole (Ⅳ'e), was expected for the product since the reaction would proceed through either course (i) or (ii) involving resonance-stabilized carbanions and the nitrile oxide (V) derived from I, as shown in Chart 2. The infrared datum, however, was not conclusive for a choice between the two structures. If the methyl ketone structure (Ⅳe) were correct, the product should react with the reagents for active methylene groups. With the several reagents (*i.e.*, sodium nitroprusside,[3] *p*-dimethylaminobenzaldehyde,[4] picric acid-sodium hydroxide[4] and sodium hypoiodite (the iodoform test[5])) the product was positive for all the reactions as shown in Table I involving the control tests carried out at the same time. Thus the results clearly demonstrated for the product to be formulated as Ⅳe, excluding the possibility of Ⅳ'e.

Similarly, 5-amino-3-(5-nitro-2-furyl)-4-isoxazolecarboxylates (Ⅳf and Ⅳg) and 5-amino-3-(5-nitro-2-furyl)-4-isoxazolecarbonitrile (Ⅳh) were obtained from sodiocyanoacetates and sodiomalononitrile, respectively. However, the reaction of sodiobenzoylacetonitrile with I gave a product showing an absorption band at 2250 cm^{-1}

Table I. Results of the Tests by the Reagents for Active Methylene Groups

Reagents \ Tested samples	Ⅳe	Ⅳd	Ⅳi	Ⅵ[b]
Sodium nitroprusside	+ (red)	+ (reddish violet)	−	−
p-Dimethylaminobenzaldehyde	+ (yellow)	+ (yellow)	−	−
Picric acid-sodium hydroxide	+ (red)	+ (red)	−	−
Sodium hypoiodite	+[a]	+[a]	−	−

a) The resulted CHI_3 was isolated.
b) 5-Ethyl-4-methyl-3-(5-nitro-2-furyl)isoxazole*2

3) F. Feigle: "Spot Tests," English ed., Vol. 2, 160 (1954), Elsevier Publ. Co., London.
4) T. Momose: "Yuki-Teisei-Bunseki," 85 (1957), Hirokawa Publ. Co., Tokyo.
5) R.L. Shriner, R.C. Fuson, D.Y. Curtin: "The Systematic Identification of Organic Compounds," 156 (1956), John Wiley & Sons, Inc., New York.

in its infrared spectrum, which was in good agreement with the formulation of 5-phenyl-3-(5-nitro-2-furyl)-4-isoxazolecarbonitrile (Ⅳi) rather than alternatively possible 5-amino-4-benzoyl-3-(5-nitro-2-furyl)isoxazole.

All attempts to hydrolize the 4-isoxazolecarboxylates (Ⅳa and Ⅳg) to the corresponding carboxylic acids under a variety of acidic conditions were unsuccessful, always resulting in a recovery of the starting ester.

In general, most of the compounds herein reported possess an excellent *in vitro* activity against both gram-positive and gram-negative bacteria and also against *Tricomonas vaginalis*. It is noteworthy that the presence of the amino group at position 5 on the isoxazole ring such as in Ⅳf, Ⅳg or Ⅳh causes an increase in the activity and that Ⅳh, in particular, is effective in controlling experimental infections in mice against both *Salmonella typhimurium* and *Staphylococcus aureus*.

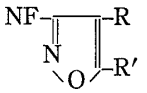
Further details of the antimicrobial activity will be published elsewhere.

Experimental*3

General Method for Preparation of 4,5-Di-substituted-3-(5-Nitro-2-furyl)isoxazoles (IV)——A solution or suspension of sodium salt of the active methylene compound [prepared from sodium (0.23 g., 10 mmoles), abs. EtOH (10 ml.) and the active methylene compound (10 mmoles)] was added slowly to a stirred solution of 5-nitro-2-furhydroxamoyl chloride[1] (I) (1.9 g., 10 mmoles) in abs. EtOH (5 ml.) at 0～5°, and the mixture was allowed to warm to room temperature for 1～2 hr. The resulting crystals were collected by filtration, washed with water and then cold MeOH, and recrystallized from an appropriate solvent. For the preparation of Ⅳa and Ⅳf, abs. MeOH was used as a solvent in place of EtOH.

The compounds (Ⅳ) thus prepared were shown in Table Ⅱ.

Table Ⅱ. 4,5-Di-substituted-3-(5-nitro-2-furyl)isoxazoles (Ⅳ);



Compound	R	R′	m.p. (°C)	Yield (%)	Recryst. solv.	Appearrance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	CO_2CH_3	CH_3	121～123	51	EtOH	pale yellow needles	$C_{10}H_8O_6N_2$	47.62	3.20	11.11	47.84	3.16	11.30
b	$CO_2C_2H_5$	CH_3	81～82	45	MeOH	yellow needles	$C_{11}H_{10}O_6N_2$	49.63	3.79	10.52	49.82	3.69	10.71
c	$CO_2C_2H_5$	C_6H_5	99～100	32	Me_2CO–EtOH	colorless needles	$C_{16}H_{12}O_6N_2$	58.54	3.68	8.53	58.44	3.65	8.62
d	$COCH_3$	CH_3	111～113	58	MeOH	yellow needles	$C_{10}H_8O_5N_2$	50.85	3.41	11.86	50.87	3.29	12.09
e	$COCH_3$	C_6H_5	131～132	40	EtOH	pale yellow prisms	$C_{15}H_{10}O_5N_2$	60.40	3.38	9.39	60.59	3.60	9.55
f	CO_2CH_3	NH_2	249～251 (decomp.)	37	Me_2CO	pale yellow prisms	$C_9H_7O_6N_3$	42.69	2.79	16.60	42.82	2.83	16.72
g	$CO_2C_2H_5$	NH_2	204～206	41	EtOH	yellow needles	$C_{10}H_9O_6N_3$	44.95	3.40	15.73	44.89	3.17	15.93
h	CN	NH_2	250 (decomp.)	50	Me_2CO–EtOH	pale yellow prisms	$C_8H_4O_4N_4$	43.64	1.83	25.45	43.76	1.99	25.69
i	CN	C_6H_5	178～180	56	Me_2CO–EtOH	pale pink needles	$C_{14}H_7O_4N_3$	59.79	2.51	14.94	59.51	2.56	15.09

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*3 All melting points were taken on a micro hot-stage apparatus and are uncorrected.