79. Haruo Saikachi, Haru Ogawa, Iwao Furukawa, and Haruhiko Hoshida : Synthesis of Furan Derivatives. XIV. Synthesis of β-(5-Nitro-2-furyl)-α-methyl-, -α-ethyl-, and -α-bromo-acrolein Derivatives.

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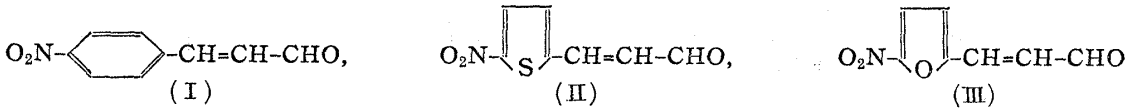
In previous papers[1] we reported the synthesis of some 2-(5-nitro)furylacrolein derivatives of the general formula NO_2-C_4H_2O-CH=CH-CH=R (R : >N-NH-, =N-C-) and that generally the compounds of this type display better antibacterial activity than that of the corresponding derivatives of 2-(5-nitro)furfurylidene type.

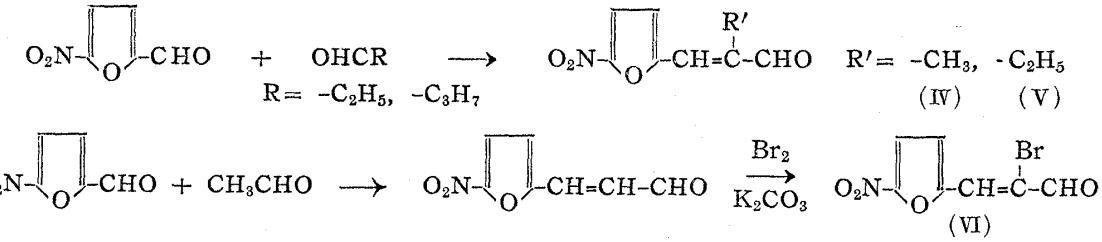
In connection with our previous work, it has been known for several years that aromatic acroleins are of biological interest.[2] Recently, Affons and Khorana[3] announced that some halogenated derivatives of cinnamic acid and *p*-nitrocinnamic acid possess a very high antibacterial activity. Furthermore, it has been reported that a number of related compounds in the *p*-nitrocinnamic series and their analogs in the thiophene series have been synthesized and especially β-(5-nitrothienyl)-α-bromoacrolein[4] has shown a marked antibacterial and fungicidal activities.

Consequently, the relation of structural resemblance between (I), (II), and (III) has prompted us to synthesize some new 2-(5-nitro)furylacrolein derivatives and to test them against microörganisms.



(I) (II) (III)

In this work, therefore, an attempt was made to synthesize β-(5-nitrofuryl)-α-methylacrolein, -α-ethylacrolein and -α-bromoacrolein, in the following manner.



Preparations of β-(5-nitro-2-furyl)-α-methylacrolein (IV) and -α-ethylacrolein (V) were carried out by the condensation of 2-(5-nitro)furfural with propionaldehyde and butyraldehyde, respectively, in the presence of piperidinium acetate as a catalyst. Synthesis of β-(5-nitro-2-furyl)-α-bromoacrolein (VI) was accomplished by the bromination in an acetic acid solution without isolating the corresponding dibromo compound owing to its instability, since hydrogen bromide was rapidly lost on standing. In practice, addition of one mole of potassium carbonate was sufficient to effect smooth elimination of hydrogen bromide.

The preparation of β-furyl-α-methylacrolein diacetate[5] (b.p_{55} 141~142°) was attempted with acetic anhydride in the presence of stannous chloride as a catalyst and

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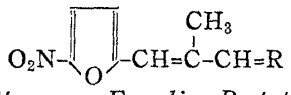
1) H. Saikachi, *et al.* : J. Pharm. Soc. Japan., **69**, 34(1949); **71**, 982(1951); **73**, 716(1955); This Bulletin, **3**, 194(1955).
2) E. Keeser, J. Houbens : "Fortschritte der Heilstoffchemie," 2. Abt., Berlins-Leipzig, 254(1932).
3) Indian J. Pharm., **14**, 3(1952).
4) J. Am. Chem. Soc., **76**, 4391(1954).
5) H. Pommer : Ann., 579(1954).

a direct nitration with acetyl nitrate, but unfortunately these attempts were unsuccessful due to the formation of a resinous matter. As noted previously, these new compounds, β-(5-nitro-2-furyl)-α-methylacrolein, -α-ethylacrolein, and -α-bromoacrolein, were synthesized in order to obtain antibacterial compounds by condensation with semicarbazide, thiosemicarbazide, 1-aminohydantoin,[6] some hydrazides, and miscellaneous amines as auxo-antibacterial groups.[1]

It is the purpose of this communication to show the relationship between the substituents at α-position of β-(5-nitro-2-furyl)acrylidene type and antibacterial activity of those compounds.

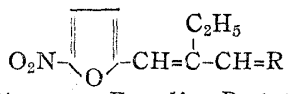
Previous investigation[1] had shown that insertion of a double bond between the aldehyde group and furan ring causes a marked increase of bacteriostatic activity. Moreover, the present work shows that substitution at α-position of 2-(5-nitro)furylacrolein exerts a more marked increase of the bactericidal activity and generally a broad spectrum of activity as may be seen from Tables I, II, and III.

Table I. Minimal Inhibitory Concentration (Unit : 10,000)



	Compound	*St. aur.*	*E. coli*	*B. typh.*	*S. dysent.*	*V. chol.*	*M. tuberc.**
(Ⅶ)	R = >N-NHCONH$_2$	16	16	1	2	64	>64
(Ⅷ)	>N-NHCSNH$_2$	8	2	1	1	8	8
(Ⅸ)	>N-NH-C(=NH)-NH$_2$·HCl	64	32	16	16	64	8
(Ⅹ)	>N-NH-CH$_2$COOC$_2$H$_5$	—	—	—	—	—	—
(Ⅺ)	>N-N(CO-NH$_2$)-CH$_2$-COOC$_2$H$_5$	16	16	4	4	64	8
(Ⅻ)	>N-N(CO-)-CH$_2$-CO-NH-	16	32	16	8	—	—
(ⅩⅢ)	>N-OH	32	64	16	16	—	>64

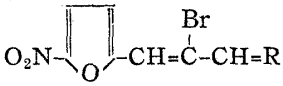
Table II. Minimal Inhibitory Concentration (Unit : 10,000)



	Compound	*St. aur.*	*E. coli*	*B. typh.*	*S. dysent.*	*V. chol.*	*M. tuberc.**
(ⅩⅣ)	R = >N-NHCONH$_2$	16	4	1	1	32	32
(ⅩⅤ)	>N-NHCSNH$_2$	1	1	1	1	1	8
(ⅩⅥ)	>N-NH-C(=NH)-NH$_2$·HCl	64	16	8	16	32	1
(ⅩⅦ)	>N-N(CONH$_2$)-CH$_2$COOC$_2$H$_5$	32	8	2	2	64	1
(ⅩⅧ)	>N-N(CO-)-CH$_2$-CO-NH-	32	16	8	8	—	—

6) H. Uoda, A. Taki: J. Pharm. Soc. Japan, **74**, 697 (1954); W. Traube, E. Hoffa: Ber., **31**, 162 (1898).

Table III. Minimal Inhibitory Concentration (Unit : 10,000)

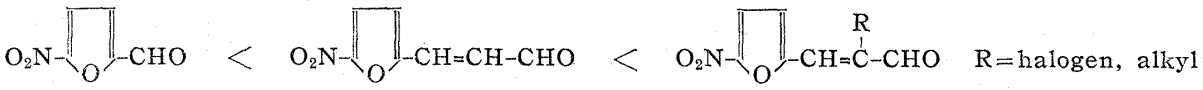


Compound	*St. aur.*	*E. coli*	*B. typh.*	*S. dysent.*	*V. chol.*	*M. tuberc.**
(XIX) R = >N-NHCONH$_2$	124	64	16	32	64	16
(XX) >N-NH-C(=NH)-NH$_2$·HCl	32	16	8	8	64	4
(XXI) >NOH	16	64	16	32	64	16
(XXII) >N-N=CH-C(Br)=CH-(5-nitro-2-furyl)	8	32	64	32	64	64
(XXIII) >N-NHCO-(benzene)	4	2	1	1	8	64
(XXIV) >N-NH-(benzene)	16	1	1	2	64	4
(XXV) >N-NHCO-(2-OH-4-NH$_2$-benzene)	16	2	1	1	64	64
(XXVI) >N-NHCO-(pyridine)	32	4	8	4	64	>64
(XXVII) >N-(2-OH-5-COOCH$_3$-benzene)	1	1	1	1	2	64
(XXVIII) >N-N(CONH$_2$)-CH$_2$COOC$_2$H$_5$	2	1	1	1	4	< 2
(XXIX) >N-N(CO-CO-NH)-CH$_2$	64	8	64	64	—	8

* Aoyama B-strain; time of incubation, 4 weeks; culture medium used; Kirchner. In other tests, the time of incubation was 96 hours.

These tests were carried out by Dr. T. Kawata and Dr. T. Tokunaga in the Department of Bacteriology, Medical Faculty, University of Kyushu.

It is interesting to note the great activity of β-(5-nitro-2-furyl)-α-methylacrolein semicarbazone (VII), β-(5-nitro-2-furyl)-α-methylacrolein oxime (XIII), and 1-[β-(5-nitro-2-furyl)-α-bromoacrylidene]-2-isonicotinylhydrazine (XXVI) against *Mycobacterium tuberculosis*. As seen from above Tables, we were mainly interested in comparing the antibacterial activity of the corresponding furfurylidene type derivatives of 2-(5-nitro)furfural with that of β-(5-nitro-2-furyl)-α-methyl-, β-(5-nitro-2-furyl)-α-ethyl-, and β-(5-nitro-2-furyl)-α-bromoacrylidene type derivatives. These furylacroleins would fall in the following order of antibacterial activity.[1)]



We wish to express our thanks and appreciation to Mr. M. Hirosawa, Mr. T. Tsukamoto (Mitsubishi Chemical Industries Ltd., Japan), Dr. H. Uoda, and Dr. S. Kato for contributing important intermediates for this work. Further, we thank Prof. Dr. T. Toda of Medical Faculty, University of Kyushu, for the micrological screening. This study was supported by a grant from the Ministry of Education.

Experimental

β-(5-Nitro-2-furyl)-α-methylacrolein—To a solution of 7.5 g. of 2-(5-nitro)furfural in 25 cc. of pure dried benzene, 6 g. of freshly distilled propionaldehyde (b.p. 50°) was added drop by drop

at 0° in an ice-salt bath and then 0.3 g. of piperidinium acetate was added. The temperature of this mixture was kept at 0° for about 1 hr. and the temperature gradually raised from 0° to 45° within 5 hrs., shielded from sunlight, and allowed to stand overnight.

After completion of the reaction, benzene was distilled off under reduced pressure and a brown viscous oily matter was obtained. A small portion of AcOH or HCl was added to the residue, washed twice with water in a separating funnel, and extracted twice with ether. Ether solution was dried over anhyd. Na_2SO_4, filtered, and the ether distilled off. Again the brown oily matter was obtained. The residue was distilled *in vacuo* and the fraction boiling at 140~145° (2 mm. Hg) was collected. Recrystallization from MeOH gave 3.2 g. of pale yellow needles, m.p. 94.5~95°; $b.p_2$ 145°. *Anal.* Calcd. for $C_8H_7O_4N$: C, 53.04; H, 3.87; N, 7.74. Found: C, 53.23; H, 3.99; N, 7.62.

β-(5-Nitro-2-furyl)-α-ethylacrolein—One gram of piperidinium acetate as catalyst was carefully added to the solution of 3.0 g. of 2-(5-nitro)furfural and 7.20 g. of butyraldehyde in 20 cc. of freshly distilled benzene at ca. 0°. The mixture was kept at room temperature for 1 hr., then the temperature was raised gradually on a water bath to 50° during 5 hrs., keeping the mixture in a dark place. After cooling, the brown oily matter was separated from the benzene solution, in some cases, in a crystalline state. After removal of benzene under reduced pressure, the brown oily residue was submitted to vacuum distillation, collecting the fraction of $b.p_{0.6}$ 145~151°. Recrystallization from MeOH gave 2.4 g. of pale yellow fine needles, m.p. 74.5~75°, which darkened on exposure to light. *Anal.* Calcd. for $C_9H_9O_4N$: N, 7.18. Found: N, 6.96.

β-(5-Nitro-2-furyl)-α-bromoacrolein—A mixture of 3 g. of 2-(5-nitro)furylacrolein (m.p. 119°) and 60 cc. glacial AcOH was heated on a water bath at 50°, added slowly with a solution containing 2.9 g. of Br_2 in 12 cc. of glacial AcOH. The temperature of this mixture was maintained at 80° on a water bath for 0.5 hr. and then treated with 3.8 g. of K_2CO_3. The temperature of this reaction mixture was raised to 90° and kept at that temperature for 1 hr., cooled with ice water, and collected by suction. The precipitate obtained was washed with water, dried carefully on a water bath, and recrystallized from abs. EtOH; yield 3.4 g. of yellow needles, m.p. 113°. *Anal.* Calcd. for $C_7H_4O_4NBr$: C, 34.16; H, 1.62; N, 5.68. Found: C, 34.42; H, 1.56; N, 5.45.

β-(5-Nitro-2-furyl)-α-methylacrolein Semicarbazone (VII)—A solution of 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein and 1.11 g. of semicarbazide hydrochloride in 20 cc. of EtOH was moderately warmed on a water bath with 1.5 g. of AcONa. After cooling, the separated product was collected by suction and recrystallized from EtOH; yield 1.5 g. of yellow plates, m.p. 240~242° (decomp.). *Anal.* Calcd. for $C_9H_{10}O_4N_4$: N, 23.53. Found: N, 23.32.

β-(5-Nitro-2-furyl)-α-methylacrolein Thiosemicarbazone (VIII)—A solution of 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein in 20 cc. EtOH was added to 1.82 g. of a 50% EtOH solution of thiosemicarbazide. A precipitate formed immediately. The mixture was heated on a water bath for 10 mins., cooled, and filtered by suction. Recrystallization from EtOH gave brown needles, m.p. 198° (decomp.). *Anal.* Calcd. for $C_9H_{10}O_3N_4S$: N, 22.00. Found: N, 22.30.

β-(5-Nitro-2-furyl)-α-methylacroleinaminoguanidine Hydrochloride (IX)—To a solution of 1.4 g. of aminoguanidine hydrogen carbonate and 0.6 g. of AcONa in 5 cc. of water, a solution of 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein in 5 cc. EtOH was added. The mixture was moderately warmed on a water bath at 40° for about 20 mins., cooled, and acidified to Congo red with conc. HCl. After cooling in an ice box, the yellow crystalline precipitate was collected by suction, washed with cold water, and recrystallized from MeOH; yield 1.3 g. of golden yellow needles, m.p. 276° (decomp.). *Anal.* Calcd. for $C_9H_{12}O_3N_5Cl$: N, 25.59. Found: N, 25.60.

β-(5-Nitro-2-furyl)-α-methylacrylidenehydrazinoethyl Acetate (X)—To a solution of 0.33 g. of hydrazinoethyl acetate hydrochloride and 0.2 g. of fused AcONa in 5 cc. of 90% EtOH, a solution of 0.4 g. of β-(5-nitro-2-furyl)-α-methylacrolein in 5 cc. of EtOH was added, the color of the mixture gradually becoming reddish. After a few mins., reddish orange crystals deposited, and the reaction mixture was allowed to stand for 4 hrs. at room temperature. The crystalline precipitate was filtered by suction, washed with cold water, and without drying, recrystallized from aq. EtOH; yield 0.12 g. of reddish orange needles; m.p. 127~128° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}O_5N_3$: C, 38.16; H, 3.52; N, 12.14. Found: C, 38.63; H, 3.35; N, 12.62.

N^1-Carbamoyl-N^2-[β-(5-nitro-2-furyl)-α-methylacrylidene]hydrazinoethyl Acetate (XI)—To a solution of 1.62 g. of hydrazinoethyl acetate hydrochloride in 5 cc. of water, 1.1 g. of KCNO was added. The mixture was heated for a few mins. and neutralized with dil. HCl. A solution of 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein in 3 cc. of EtOH was added to the mixture, the mixture was heated on a water bath for a few mins., cooled with ice, and filtered by suction. Recrystallization from a mixture of EtOH and water (3 : 2) gave 0.4 g. of pale greenish yellow needles, m.p. 236°. *Anal.* Calcd. for $C_{13}H_{16}O_6N_4$; N, 17.28. Found: N, 17.54.

β-(5-Nitro-2-furyl)-α-methylacrolein-1-aminohydantoin (XII)—Method (a): A solution of 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein in 6 cc. of EtOH was added to the solution of 0.22 g. of 1-aminohydantoin hydrochloride (m.p. 203~204° (decomp.)) in 5 cc. of water, the mixture was heated

on a water bath, when it became clear, and a reddish crystalline precipitate deposited after a few minutes. After cooling on ice, the precipitate was collected by suction and recrystallized from EtOH; yield 0.4 g. of reddish crystalline mass, m.p. 270°(decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_5N_4$: N, 20.22. Found : N, 19.81.

Method(b) : A solution of 1 g. of KCNO in 5 cc. of water was added to 3 g. of hydrazinoethyl acetate hydrochloride and refluxed for a few mins. After adding 35 cc. of 30% H_2SO_4, the mixture was refluxed for an additional 1 hr. After rapid cooling, 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein in 5 cc. of EtOH was added to this solution, the mixture was moderately warmed on a water bath for 20 mins., cooled in an ice-salt bath, the precipitate was collected, and recrystallized twice from EtOH; yield, 0.35 g. of reddish crystalline mass, m.p. 263~269°(decomp.).

β-(5-Nitro-2-furyl)-α-methylacrolein Oxime (XIII)—To a solution of 1.91 g. of β-(5-nitro-2-furyl)-α-methylacrolein dissolved in 15 cc. of EtOH, a filtered solution of 0.7 g. of hydroxylamine hydrochloride and 0.5 g. of fused AcONa in 10 cc. of water was added. The mixture was moderately heated on a water bath for about 20 mins. After cooling on ice, the yellow crystalline precipitate was collected by suction and recrystallized from 80% EtOH to 0.8 g. of yellow crystals, melting at 149°. *Anal.* Calcd. for $C_8H_8O_4N_2$: N, 14.29. Found : N, 14.52.

β-(5-Nitro-2-furyl)-α-ethylacrolein Semicarbazone (XIV)—A solution of 2.05 g. of β-(5-nitro-2-furyl)-α-ethylacrolein in 20 cc. of EtOH was added to a solution of 1.1 g. of semicarbazide hydrochloride and 1.5 g. of fused AcONa in 20 cc. of water. The mixture was allowed to stand for 1 hr. at room temperature and moderately heated on a water bath for 10 mins. After cooling, the crystalline precipitate was collected by suction and recrystallized from EtOH; yield 1.2 g. of yellow needles, m.p. 209°. *Anal.* Calcd. for $C_{10}H_{12}O_4N_4$: N, 22.22. Found : N, 21.97.

β-(5-Nitro-2-furyl)-α-ethylacrolein Thiosemicarbazone (XV)—To a solution of 2.05 g. of β-(5-nitro-2-furyl)-α-ethylacrolein in 20 cc. of EtOH, 1.9 g. of a 50% EtOH solution of thiosemicarbazide was added. The mixture was heated at 50° on a water bath for 20 mins., allowed to stand for 1 hr. in an ice-water bath, and the yellow precipitate was collected. Recrystallization from MeOH yielded 1.2 g. of orange yellow needles, m.p. 205°(decomp.). *Anal.* Calcd. for $C_{10}H_{12}O_3N_4S$: N, 20.82. Found : N, 21.34.

β-(5-Nitro-2-furyl)-α-ethylacroleinaminoguanidine Hydrochloride (XVI)—A solution of 2.05 g. of β-(5-nitro-2-furyl)-α-ethylacrolein in 7 cc. of EtOH was added to a solution of 1.4 g. of aminoguanidine hydrogen carbonate and 0.6 g. of AcONa in 5 cc. of water. The mixture was moderately warmed on a water bath at 40° for 20 mins. After stirring at room temperature for 30 mins., the resulting mixture was strongly acidified with conc. HCl, cooled thoroughly in an ice box, the resulting yellow crystalline precipitate was collected by suction, and washed with cold water. The yellow precipitate, after drying, melted at 205~206°(decomp.). This compound was purified by recrystallization from MeOH to 1.3 g. of golden yellow needles, m.p. 212~214°(decomp.). *Anal.* Calcd. for $C_{10}H_{14}O_3N_5Cl$: N, 24.35. Found : N, 24.08.

N^1-Carbamoyl-N^2-[β-(5-nitro-2-furyl)-α-ethylacrylidene]hydrazinoethyl Acetate (XVII)—One gram of KCNO was added to a solution of 1.62 g. of hydrazinoethyl acetate hydrochloride in 2.5 cc. of water and the mixture was heated on a water bath for a few mins. After cooling, the mixture was carefully neutralized with a small amount of dil. HCl and a solution of 2.05 g. of β-(5-nitro-2-furyl)-α-ethylacrolein in 5 cc. of EtOH was added to the mixture, the mixture was heated on a water bath for 10 mins., and allowed to stand at room temperature in a dark place overnight. The yellow precipitate obtained was collected and recrystallized, after drying, from aq. EtOH; yield, 0.3 g. of fine yellow crystals, m.p. 212°(decomp.). *Anal.* Calcd. for $C_{14}H_{18}O_6N_4$: N, 17.71. Found : N, 17.64.

β-(5-Nitro-2-furyl)-α-ethylacrolein-1-aminohydantoin (XVIII)—A solution of 0.22 g. of 1-aminohydantoin hydrochloride (m.p. 203~204°(decomp.)) in 5 cc. of water was added to a solution of 0.22 g. of β-(5-nitro-2-furyl)-α-ethylacrolein in 6 cc. of EtOH. The mixture was heated on a water bath at 60° for 10 mins., cooled, and the crystalline product obtained was recrystallized from EtOH; yield, 0.3 g. of reddish brown crystals, m.p. 265°(decomp.). *Anal.* Calcd. for $C_{12}H_{11}O_5N_4$: N, 19.24. Found : N, 18.91.

β-(5-Nitro-2-furyl)-α-bromoacrolein Semicarbazone (XIX)—To 0.51 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 10 cc. of 95% EtOH, a solution of 0.22 g. of semicarbazide hydrochloride and 0.35 g. of AcONa in 10 cc. of 95% EtOH was added and the mixture kept for 30 mins. at room temperature, when yellow crystalline precipitate separated. The product obtained was collected by suction, washed with water, and recrystallized from EtOH; yield, 0.4 g. of yellow prisms, m.p. 250°(decomp.). *Anal.* Calcd. for $C_8H_7O_4N_4Br$: C, 32.00; H, 2.33; N, 18.66. Found : C, 31.82; H, 2.00; N, 18.60.

β-(5-Nitro-2-furyl)-α-bromoacroleinaminoguanidine Hydrochloride (XX)—A solution of 2.5 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 10 cc. of EtOH was added to a solution of 1.10 g. of aminoguanidine hydrochloride (m.p. 163°) in 5 cc. of water, when bright yellow crystals deposited

gradually. The crystals were collected by suction and recrystallized from abs. EtOH; yield, 0.28 g. of bright yellow needles, m.p. 258°(decomp.). *Anal.* Calcd. for $C_6H_6O_3N_5Br \cdot HCl$: C, 28.37; H, 2.91; N, 20.71. Found: C, 28.48; H, 2.93; N, 20.52.

β-(5-Nitro-2-furyl)-α-bromoacrolein Oxime (XXI)—A solution of 1.25 g. of β-(5-nitro-2-furyl)-α-bromoacrolein and 0.35 g. of hydroxylamine hydrochloride (m.p. ca. 149~150°) in 10 cc. of 80% EtOH was treated with 0.4 g. of AcONa. After standing at room temperature for 1 hr., a yellow crystalline mass obtained was filtered by suction and recrystallized from EtOH; yield, 0.12 g. of light yellow needles, m.p. 207°(decomp.). *Anal.* Calcd. for $C_7H_5O_4N_2Br$: C, 32.20; H, 1.93; N, 10.72. Found: C, 32.15; H, 1.83; N, 10.32.

Bis[β-(5-nitro-2-furyl)-α-bromoacrylidene]hydrazine (XXII)—A solution of 1.25 g. of β-(5-nitro-2-furyl)-α-bromoacrolein and 0.32 g. of 80% hydrazine hydrate in 20 cc. of EtOH was moderately warmed on a water bath at 40° for 10 mins. An orange yellow precipitate formed immediately. The product formed was collected by suction and recrystallization from EtOH gave 0.5 g. of yellow needles, m.p. 211~212°(decomp.). *Anal.* Calcd. for $C_{14}H_8O_6N_4Br_2$: N, 11.84. Found: N, 12.04.

β-(5-Nitro-2-furyl)-α-bromoacrylidene Benzoylhydrazide (XXIII)—To a solution of 1.25 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 10 cc. of EtOH, a solution of 0.4 g. of benzoylhydrazide (m.p. 114°) in 5 cc. of AcOEt was added and a yellow crystalline mass separated from the reaction mixture when warmed on a water bath for a few mins. After cooling and filtering, recrystallization from EtOH gave 0.5 g. of bright yellow prisms, m.p. 182°. *Anal.* Calcd. for $C_{14}H_{10}O_4N_3Br$: C, 46.10; H, 2.78; N, 11.25. Found: C, 46.10; H, 2.95; N, 10.99.

β-(5-Nitro-2-furyl)-α-bromoacroleine Phenylhydrazone (XXIV)—To a solution of 0.26 g. of phenylhydrazine in 5 cc. of EtOH, a solution of 0.59 g. of β-(5-nitro-2-furyl)-α-bromoacrolein was added. After standing for 30 mins. at room temperature, a reddish needle-like crystalline mass formed, which were collected by suction, washed with cold water, and without drying, recrystallized from EtOH. This procedure gave 0.38 g. of dark red needles, m.p. 107°(decomp.). *Anal.* Calcd. for $C_{13}H_{10}O_3N_3Br$: C, 46.55; H, 3.01; N, 12.55. Found: C, 46.33; H, 2.86; N, 12.82.

β-(5-Nitro-2-furyl)-α-bromoacrolein p-Aminosalicyloylhydrazone (XXV)—To a solution of 0.25 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 5 cc. of EtOH, a solution of 0.4 g. of *p*-aminosalicyloylhydrazide (m.p. 198~200°) in 5 cc. EtOH was added drop by drop. The mixture was warmed at 50° on a water bath for a few mins. and a reddish yellow granular mass deposited. After cooling on ice, the mass was collected by suction and recrystallized from a mixture of AcOEt and acetone (1 : 3); yield, 0.28 g. of a slightly reddish orange granular mass melting at 207° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_5N_4Br$: N, 11.95. Found: N, 12.14.

As the reaction of diazonium salt of this final product with aq. alkaline solution of β-naphthol developed a reddish orange color, it was proved that the final condensation product reacted only with hydrazino group of *p*-aminosalicyloylhydrazide.

1-[β-(5-Nitro-2-furyl)-α-bromoacrylidene]-2-isonicotinylhydrazine (XXVI)—To a solution of 0.5 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 10 cc. of EtOH, 0.27 g. of isonicotinylhydrazine dissolved in 5 cc. of water was added. The mixture was heated on a water bath at 60° for 15 mins., cooled on ice, the yellow crystalline precipitate was collected by suction, and washed well with cold water. One recrystallization from MeOH gave 0.22 g. of pale yellow needles, m.p. 234~235° (decomp.). *Anal.* Calcd. for $C_{13}H_9O_4N_4Br$: C, 42.74; H, 2.49; N, 15.34. Found: C, 42.73; H, 2.58; N, 15.06.

β-(5-Nitro-2-furyl)-α-bromoacrylidene Methyl p-Aminosalicylate (XXVII)—To a solution of 0.59 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 5 cc. of EtOH, a solution of 0.54 g. of methyl *p*-aminosalicylate in 5 cc. of EtOH was added drop by drop. The mixture was moderately heated on a water bath for ca. 20 mins., stood for 3 hrs. at room temperature, and the deposited mass was collected and recrystallized from AcOEt; yield, 0.4 g. of bright yellow needles, m.p. 185~186°. *Anal.* Calcd. for $C_{15}H_{11}O_6N_2Br$: C, 45.59; H, 2.80; N, 7.09. Found: C, 45.64; H, 2.77; N, 7.58.

N^1-Carbamoyl-N^2-[β-(5-nitro-2-furyl)-α-bromoacrylidene]hydrazinoethyl Acetate (XVIII)—To a solution of 0.5 g. of hydrazinoethyl acetate hydrochloride in 3 cc. of water, 0.3 g. of KCNO was added, and heated on a water bath for ca. 5 mins. The mixture obtained was added drop by drop to a solution of 0.2 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 5 cc. of EtOH. On cooling with ice water, yellow crystalline precipitate deposited immediately, which was filtered by suction and washed thoroughly with a mixture of water and EtOH (1 : 3). Recrystallization of this crude precipitate from abs. EtOH gave 0.2 g. of pale yellow needles, m.p. 235°(decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_6N_4Br$: C, 37.02; H, 3.37 ; N, 14.39. Found: C, 36.99; H, 3.24; N, 14.12.

β-(5-Nitro-2-furyl)-α-bromoacrylidene-1-aminohydantoin (XXIX)—A solution of 0.56 g. of β-(5-nitro-2-furyl)-α-bromoacrolein in 6 cc. of EtOH was added to a solution of 0.22 g. of 1-aminohydantoin hydrochloride (m.p. 203~204°) in 5 cc. of water and the mixture was heated on a water bath, when the reaction mixture gradually became clear and after a few minutes a yellow crys-

talline precipitate deposited. After cooling on ice, the precipitate was collected by suction and recrystallized from dioxane; yield, 0.21 g. of slightly greenish yellow prisms, m.p. 265°(decomp.). *Anal.* Calcd. for $C_{10}H_7O_5N_4Br$: N, 16.36. Found : N, 16.05.

Summary

β-(5-Nitro-2-furyl)-α-methylacrolein and β-(5-nitro-2-furyl)-α-ethylacrolein were prepared by the condensation of 2-(5-nitro)furfural with propionaldehyde and butyraldehyde, respectively, in the presence of piperidinium acetate as a catalyst. Preparation of β-(5-nitro-2-furyl)-α-bromoacrolein was accomplished by bromination in the usual manner.

These new compounds were used as an antibacterial group in the preparation of Schiff bases with semicarbazides, hydrazides, and amines, and then antibacterial screening of these bases was carried out.

From the screening results, β-(5-nitro-2-furyl)-α-methylacrolein semicarbazone, β-(5-nitro-2-furyl)-α-methylacrolein oxime, and 1-[β-(5-nitro-2-furyl)-α-bromoacrylidene]-2-isonicotinylhydrazine were found to exert great activity against tubercle bacilli.

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80. **Sunao Furukawa** : Reaction of 2,4-Lutidine 1-Oxide and 2,4-Dimethylquinoline 1-Oxide with Acetic Anhydride.

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Previously, Boekelheide and Linn[1] and Kobayashi and Furukawa[2] succeeded independently in converting the active methyl group in the 2- or 4-position of pyridine ring into the hydroxymethyl group by rearrangement with acetic anhydride through their N-oxide compound. In this reaction, it is clear that the methyl group in 2-position is able to react more easily than that in 4-position from the yields of the hydroxymethyl compounds prepared by rearrangement of 2- and 4-picoline 1-oxide, quinaldine 1-oxide, and lepidine 1-oxide.[3] Further, for the confirmation of these results, the present author experimented the rearrangement reaction with acetic anhydride of 2,4-lutidine 1-oxide and 2,4-dimethylquinoline 1-oxide, with active methyl groups in both 2- and 4-positions.

2,4-Lutidine 1-oxide was reacted with acetic anhydride, followed by hydrolysis with dilute hydrochloric acid, and three reaction products were isolated by repeated fractional distillation, (I) $b.p_4$ 100~107°, (II) $b.p_4$ 131~140°, and (III) $b.p_4$ 140~150°.

These three fractions, (I), (II), and (III), formed picrates melting at 156~158°, 155~157°, and 242~244°, respectively. Although the melting points of the picrates of (I) and (II) were similar, they depressed on admixture.

(I) and (II) were converted to the corresponding chloromethyl compounds with phosphorus trichloride. (I) was oxidized to 4-methylpicolinic acid and (II) to 2-methylisonicotinic acid by oxidation with calculated amount of potassium permanganate. Considering such results, it is certain that (I) is 4-methyl-2-hydroxymethylpyridine and (II) is 2-methyl-4-hydroxymethylpyridine. (III) colored red with

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2) G. Kobayashi, S. Furukawa : This Bulletin, **1**, 347(1953).
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