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Dihydrolinalool (XI)—15 g. (ca. 0.2 mole) of methyl ethyl ketone and 50 cc. of ether were added dropwise to the Grignard reagent (prepared from 21.5 g. (0.13 mole) of (X), 5 g. (ca. 0.2 mole) of Mg, and 20 cc. of dry ether) under vigorous stirring at $-5°$ to $0°$. The reaction product was treated by the usual method. b.p$_{11}$ 82～83°, d_4^{14} 0.8687, n_D^{19} 1.4415. Yield, 11.5 g. (56%). *Anal.* Calcd. for $C_{10}H_{20}O$: C, 76.92; H, 12.8. Found: C, 76.94; H, 12.87.

Grignard Reaction of Methyl Vinyl Ketone and (X)—From 33 g. (0.2 mole) of (X), 7.5 g. (ca. 0.3 mole) of metallic magnesium, and 21 g. (0.3 mole) of methyl vinyl ketone (prepared according to Hagemeyer[12] and others[13～17] under the same conditions as described above) 20 g. of a colorless liquid with a characteristic odor was obtained. It boiled at 70～75°/13 mm. 2,4-Dinitrophenylhydrazone, m.p. 192～194°. Doenigé's reagent gave no reaction. Further examination of this compound was not carried out.

Summary

Dihydrolinalool was synthesized from levulic acid and its yield was 12% of the theory.

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12) J. Am. Chem. Soc., 71, 119 (1949).
13) Oda: Synth. Chemistry (Japan) 203.
14) Morgan, Holmes: J. Chem. Soc., 1932, 2669.
15) While, Howard: J. Am. Chem. Soc., 65, 25 (1943).
16) Wingfood: C. A. 38, 2349 (1944).
17) de Fen Macquillin: J. Am. Chem. Soc., 59, 53 (1937).

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25. **Tadashi Sasaki**: Synthesis of Nitrofuroic and Nitrofurylacrylic Hydrazides and their Derivates.*

(*Institute of Scientific Research for Practical Life, Medical Faculty, University of Kyoto***)

An extensive study has been undertaken to find new antituberculous compounds having the structure of an acid hydrazide or its derivatives since the discovery of isonicotinic hydrazide[1]. Several different methods have been used on the syntheses of furoic hydrazide[2], but there is no report pertaining to the preparation of the acid hydrazides having an antibacterial nitrofuryl radical. For this reason, a synthesis of nitrofuroic and nitrofurylacrylic hydrazides was attempted.

Nitrofuroic hydrazide was easily obtained by mixing methyl or ethyl nitrofuroate with hydrazine hydrate under cooling and by using ethanol or methanol as an additional solvent[3]. The reaction was spontaneous and exothermic. Diacylhydrazine, however,

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** Yoshida-konoe-cho, Sakyo-ku, Kyoto (佐々木 正).

[1] H. L. Yale, *et al.*: J. Am. Chem. Soc., 75, 1933 (1953); Am. Rev. Tuberc., 65, 357 (1952); 67, 354 (1953).

[2] Org. Reactions, 3, 435 (1946).

[3] Furoic, methylfuroic, and bromofuroic hydrazides had already been prepared from their esters by heating without any solvent (cf. footnote 2). This fact shows that the reaction condition varies according to the individual reactivity and the introduction of a strong negative nitro radical strengthens the activity of the ester in this reaction.

could not be produced by this method so this was prepared by the application of acid hydrazide on its acid chloride by heating with pyridine as a solvent. Since nitrofurylacrylic ester was inactive against hydrazine hydrate even when heated for a long time, its acid hydrazide was obtained by the reaction of its acid chloride and hydrazine hydrate with benzene as a solvent under cooling with water. Its diacylhydrazine was obtained as a by-product in this reaction. Several derivatives produced from the acid hydrazide are summarized in Fig. 1 and their antibacterial properties are shown in Table I, but no remarkable bactericidal activity could be observed. Furthermore, the derivatives of nitrofurylacrylic hydrazide were so difficultly soluble in water that their bactericidal tests could not be carried out.

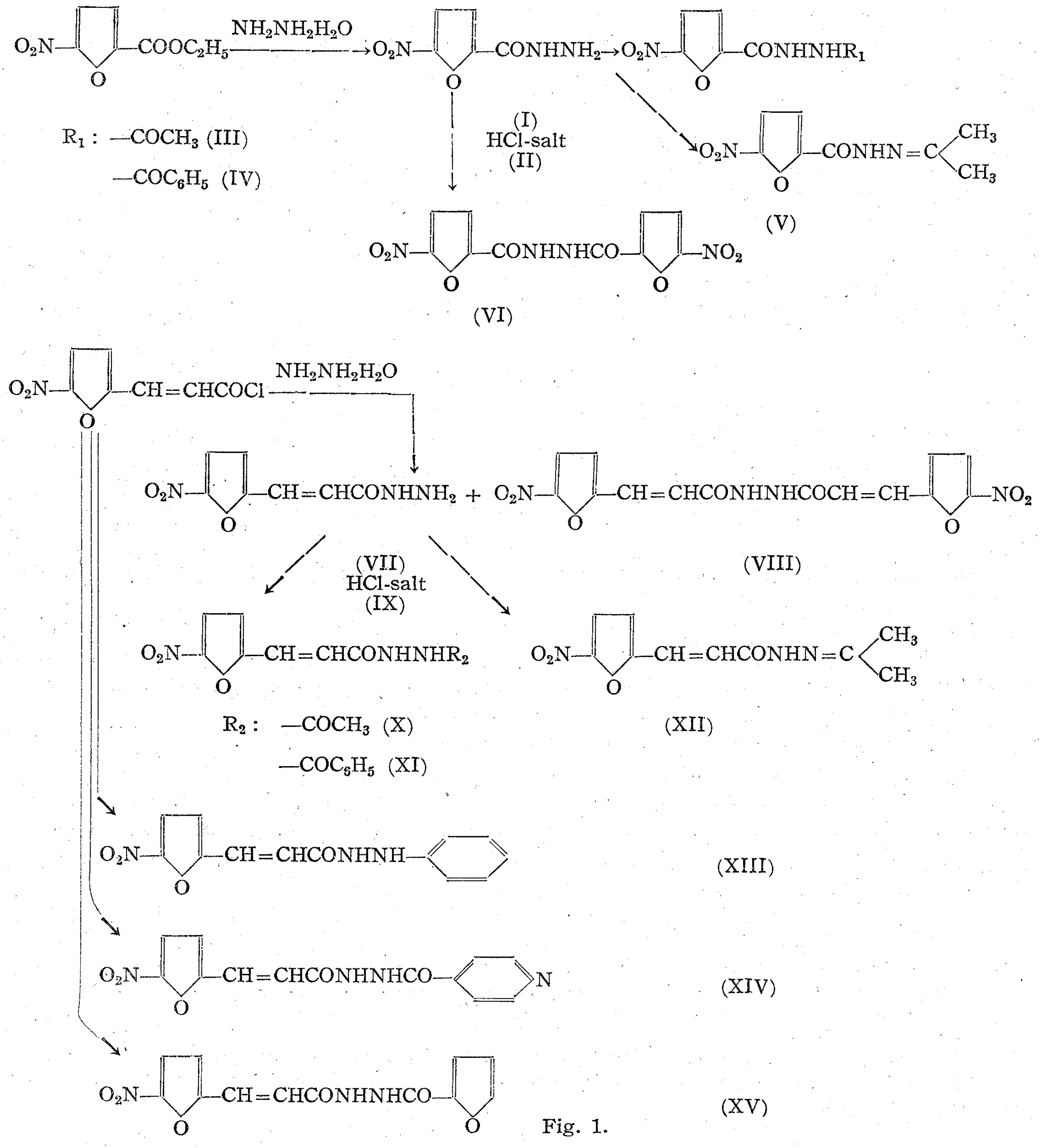

Fig. 1.

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TABLE I.

Antibacterial Action of Nitrofuroic and Nitrofurylacrylic Hydrazides*

Compound	*Staph. aur.*	*B. pyocyan.*	*B. proteus*	*E. coli*	*Eber. typh.*	*S. dysent.*	*B. subt.*
I	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	1
III	<0.5	<0.5	1	<0.5	<0.5	<0.5	<0.5
IV	1	<0.5	<0.5	4	4	2	2
IX	4	—	—	4	—	—	—
Nitrofuroic Amide	1	<0.5	<0.5	1	1	1	1

(unit 10,000; time of incubation 72 hours; culture medium used, boillon at pH 7.2)

*) Tests were carried out by Mr. A. Ohyama in the Dept. of Microbiology, Medical Faculty, University of Kyoto.

Remarks: Compounds VI, VII, VIII, X and XI were insoluble in 5,000 volumes of water and their tests were impossible.

The author expresses his gratitude to Prof. H. Saikachi for his kind advices and also to the Ministry of Education which provided the funds to enable him to carry out this expriment through the Scientific Research Fund. Elementary analysis was carried out by Miss H. Iwata of Kyoto University.

Experimental

2-(5-Nitro)-furoic Hydrazide (I)[1]—While being stirred and being cooled by ice water, 1 g. of hydrazine hydrate, b.p. 106~108°, in 10 cc. of 98% alcohol was added to a suspension of 3 g. of ethyl nitrofuroate, m.p. 101°, in 40 cc. of 98% alcohol. The temperature was gradually raised to 10° in 3 hours, then brought to room temperature after 2 hours. After letting this solution stand overnight at room temperature (20°), it was cooled to 0°, and the precipitated mass was filtered and recrystallized from ethanol to give 1.66 g. of colorless cylindrical crystals, m.p. 169~170°. *Anal.* Calcd. for $C_5H_5O_4N_3$: C, 35.08; H, 2.95; N, 24.56. Found: C, 35.43; H, 3.14; N, 24.59.

The hydrochloride (II) was prepared by dissolving 2-(5-nitro)-furoic hydrazide (I) in dil. HCl and then by evaporating the solvent. The residue was recrystallized from a small amount of abs. ethanol to give colorless crystals, m.p. 186° (decomp).

Acetyl Derivative (III) of 2-(5-Nitro)-furoic Hydrazide (I)—3 g. of acid hydrazide (I) was mixed with 5 cc. of acetic anhydride which resulted in a spontaneous exothermic reaction. The mixture was gently heated for 30 minutes over direct flame until it was completely dissolved. The solution was filtered while hot and then left to stand. Light yellow crystals were obtained which were recrystallized from ethanol to give 2 g. of colorless granular crystals, m.p. 189.5°. *Anal.* Calcd. for $C_7H_7O_5N_3$: N, 19.72. Found: N, 20.24.

Benzoyl Derivative (IV) of 2-(5-Nitro)-furoic Hydrazide (I)—In accordance with the regular method for the Schotten-Baumann reaction, 0.3 g. of the acid hydrazide (I) was benzoylated with 0.3 g. of benzoyl chloride in the presence of dil. alkali. The resulting crude crystals were recrystallized from acetic acid to give 0.4 g. of colorless plate crystals, m.p. 206° (decomp.). *Anal.* Calcd. for $C_{12}H_9O_5N_3$: N, 15.27. Found: N, 15.29.

Condensate of 2-(5-Nitro)-furoic Hydrazide with Acetone (V)—0.5 g. of acid hydrazide (I) was mixed with 5 cc. of dry acetone which resulted in an exothermic reaction. After the hydrazide was completely dissolved in acetone, the white mass again precipitated. This mixture was heated gently in a water bath to complete the reaction. It was then left to stand at room temperature and upon cooling, formed crystals, which were recrystallized from benzene to give 0.4 g. of light yellow crystals, m.p. 185~186° (decomp.). *Anal.* Calcd. for $C_8H_9O_4N_3$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.67; H, 4.07; N, 20.24.

1,2-Bis(2-(5-Nitro)-furoic) Hydrazine (VI)—0.9 g. of nitrofuroyl chloride, m.p. 38°, was mixed with 5 cc. of dry pyridine under cooling to give a white pyridinium salt. To this mixture was added 0.7 g. of acid hydrazide (I) and the resulting mixture was heated in a water bath under reflux. After 5 hours, the color of the reaction mixture changed to brown. 30 cc. of water was added to this mixture and the resulting precipitate was filtered and recrystallized twice from an ethanol-water mixture to give 0.8 g. of light brown crystals, m.p. 236° (decomp.). *Anal.* Calcd. for $C_{10}H_5O_8N_2$: C, 38.70; H, 1.94; N, 18.10. Found: C, 38.69; H, 2.30; N, 17.77.

Other methods were employed in the preparation of compound (VI) and found to be applicable, e.g. the reaction of an acid chloride on hydrazine or the oxidation of an acid hydrazide in the presence of I_2 or HgO.

2-(5-Nitro)-furylacrylic Hydrazide (VII) and 1,2-Bis(2′-(5′-Nitro)-furylacrylic) Hydrazine (VIII)—While being cooled by water to 10°, a solution of 1 cc. of hydrazine hydrate was added dropwise under stirring to a solution of 1 g. nitrofurylacrylic chloride* in 10 cc. of dry benzene. The reaction mixture changed its color from yellow to red, and red crystals began to precipitate. After the addition of hydrazine solution was over, the excess of hydrazine hydrate was neutralized with acetic acid, and the resulting yellow crystals were filtered and washed several times with water. The crystalline mass was mixed with dil. HCl and filtered once more. After neutrallization with aq. Na_2CO_3 and after being recrystallized twice from ethanol, 0.55 g. yellow crystals (VII), m.p. 203~204° (decomp.), were obtained from the filtrate. After recrystallization from acetic acid, 0.45 g. of yellow crystals (VIII), m.p. 289~290° (decomp.), were obtained from the dil. HCl-insoluble portion. *Anal.* Calcd. for $C_7H_7O_4N_3$ (VII): C, 42.63; H, 3.55; N, 21.31. Found: C, 42.39; H, 3.21; N, 21.00. *Anal.* Calcd. for $C_{14}H_{10}O_8N_4$ (VIII): C, 46.41; H, 2.76; N, 15.46. Found: C, 46.25; H, 2.55; N, 15.25.

By utilizing the same procedure as for the preparation of (II) a light yellow hydrochloride (IX), m.p. 183~188° (decomp.), was obtained from the portion soluble in dil. HCl.

Acetyl Derivative (X) of 2-(5-Nitro)-furylacrylic Hydrazide (VII)—A mixture of 0.1 g. of the acid hydrazide (VII) and 5 cc. of acetic anhydride was gently heated over a direct flame for about 1 hour. After letting it stand to cool, 20 cc. of water was added to this solution to produce light yellow crystals, which were recrystallized from ethanol to give 0.07 g. of light yellow crystals, m.p. 278° (decomp.). *Anal.* Calcd. for $C_9H_9O_5N_3$: N, 17.57. Found: N, 17.01.

Benzoyl Derivative (XI) of 2-(5-Nitro)-furylacrylic Hydrazide (VII)—0.8 g. of benzoyl chloride and 4 drops of 40% NaOH solution were added alternately at 0° under stirring to a suspension of 1 g. of acid hydrazide (VII) in 5 cc. of alcohol. The crude product, obtained by the removal of the solvent, was recrystallized from acetic acid to give 0.8 g. of colorless crystals, m.p. 275~280° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_5N_3$: N, 13.95. Found: N, 13.47.

Condensate of 2-(5-Nitro)-furoic Hydrazide with Acetone (XIII)—0.5 g. of the acid hydrazide (VII) was mixed with 10 cc. of dry acetone and the mixture refluxed in a water bath for 2 hours. After cooling, the resulting precipitate was filtered and recrystallized from alcohol to give 0.3 g. of colorless granular powder, m.p. 188~189° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_4N_3$: N, 17.72. Found: N, 17.59.

2-(5-Nitro)-furylacrylic Phenylhydrazide (XIII)—0.6 cc. of phenylhydrazine, b.p. 244°, was added to a solution of the acid chloride (0.4 g.) in 5 cc. of dry benzene whereby an exothermic reaction and precipitation took place. After letting this stand overnight, the mixture was filtered and washed with ethanol to give 0.37 g. of colorless crystals, m.p. 195° (decomp.), after recrystallization from ethanol. *Anal.* Calcd. for $C_{13}H_{11}O_4N_3$: N, 15.38. Found: N, 15.08.

2-(5-Nitro)-furylacrylic Isonicotinyl Hydrazide (XIV)—To a solution of 0.2 g. of the acid chloride in 5 cc. of dry ether was added 0.2 g. of isonicotinic acid hydrazide (Commercial product), m.p. 175°. One drop of pyridine was then added to this mixture which resulted in an immediate reaction. After letting this stand overnight, the residual mass was filtered and recrystallized twice from ethanol to give 0.1 g. of white needle crystals, m.p. 213~214° (decomp.). *Anal.* Calcd. for $C_{12}H_{10}O_4N_4$: N, 18.56. Found: N, 18.14.

2-(5-Nitro)-furylacrylic Furoylhydrazide (XV)—Utilizing the same procedure as above, from 0.4 g. of acid choloride and 0.2 g. of furoic hydrazide[4], m.p. 30~34°, was obtained 0.3 g. of crude yellow crystals, which were recrystallized from a large amount of alcohol to a yellow powder, m.p. 270° (blackening). *Anal.* Calcd. for $C_{12}H_9O_6N_3$: N, 14.43. Found: N, 14.32.

Summary

The preparation of acid hydrazides having antibacterial nitrofuryl radical was attempted, but being the derivatives of nitrofurylacrylic acid insoluble in water, the antibacterial tests of these compounds could not be carried out.

(Recieved February 22, 1954)

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*) A crude product prepared by the reaction of nitrofurylacrylic acid, m.p. 236° (decomp.), and $SOCl_2$, and removing the excess of $SOCl_2$ under reduced pressure, was used.