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Kinji Harada[*1] **and Sakae Emoto** : Studies on Nitrofuran Derivatives and Their Analogues. II.[*2] Separation and Determination of *cis*- and *trans*-1-(5-Nitro-2-furyl)-2-methylthioethylene.

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Previously it was reported[1)] that the geometrically isomeric mixture (I) of 1-(5-nitro-2-furyl)-2-methylthioethylene was prepared by the condensation of 5-nitro-2-furaldehyde with methylthioacetic acid followed by the decarboxylation over copper chromite in freshly distilled quinoline. This paper deals with the separation and the determination of the *cis* and *trans* isomers of I. Moreover the relation between their configurations and their bacteriostatic and fungistatic activities is described.

The product I seemed to be a stereoisomeric mixture by thin-layer chromatography on aluminum oxide G (Research Specialties Co.) and the melting point of I did not give a constant value after several times of recrystallization from carbon tetrachloride. The behavior of I in a number of solvents was examined in thin-layer chromatography on aluminum oxide G in order to distinguish one spot from the other more clearly. As a result, petroleum ether : ethyl acetate=20:1 was found to be a more useful solvent at room temperature and the spots were detected by their fluorescence under ultraviolet light. On the other hand, when I was dissolved in a little volume of carbon disulfide and the solution was allowed to stand at room temperature in an open vessel, yellowish brown slender needles (Ia) appeared with reddish brown crystalline product. Recrystallization of Ia, separated mechanically, from carbon disulfide gave m.p. 75.5°, showing one spot which corresponded to the lower spot of the two of I on thin-layer chromatogram. The reddish brown raw substance was chromatographed on a column of neutral alumina (M · Woelm · Eschwege) of about three hundred times of the sample in weight with the same solvent system as in thin-layer chromatography. Pale yellow plate (Ib), m.p. 86～86.5° of which spot corresponded to the upper spot of I on thin-layer chromatogram was obtained. The mixed melting point of Ib with Ia depressed to 68～70°. Moreover, the infrared absorption spectrum of Ib was clearly different from that of Ia in its fingerprint region as shown in Fig. 1.

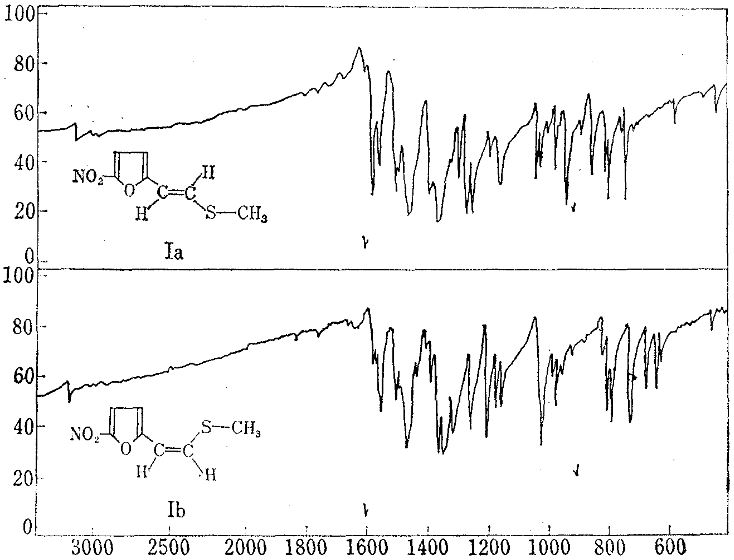

Fig. 1. Infrared Absorption Spectra (in KBr) of ***trans***-1-(5-Nitro-2-furyl)-2-methylthioethylene and ***cis***-1-(5-Nitro-2-furyl)-2-methylthioethylene

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[*2] Previous paper, "Condensation of 5-Nitro-2-furaldehyde with 4-Methyl(or 4-Ethyl)pyridine," This Bulletin, **13**, 389 (1965), represents Part I of this series.

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1) Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan, Tokushima, October, 1965.

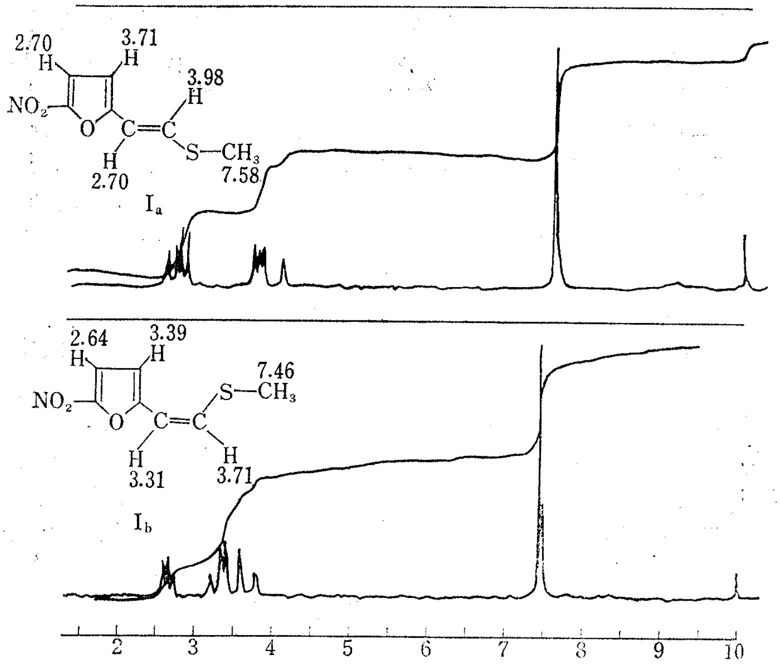

Fig. 2. Nuclear Magnetic Resonance Spectra (60 Mc.) of *trans*-1-(5-Nitro-2-furyl)-2-methylthioethylene and *cis*-1-(5-Nitro-2-furyl)-2-methylthioethylene in Deuteriochloroform using Tetramethylsilane as Internal Standard at 10 (τ-value)

Successively, the configurations of Ia and Ib will be discussed by the comparative studies of the nuclear magnetic resonance spectra (Fig. 2) and the ultraviolet absorption spectra (Fig. 3) of them.

In the nuclear magnetic resonance spectra, the structure of Ia was assigned as follows: methylthio group (τ 7.58 singlet), two protons on the nitrofuran ring (τ 2.70 and 3.71 each doublet J=3.6 c.p.s.) and two protons on the disubstituted ethylene(τ2.70 and 3.98 each doublet J=15.6 c.p.s.), while that of Ib was assigned as follows: methylthio group (τ 7.46 singlet), two protons on the nitrofuran ring (τ 2.64 and 3.39 each doublet J=3.6 c.p.s.) and two protons on the disubstituted ethylene (τ 3.31 and 3.71 each doublet J=11.4 c.p.s.).

On the basis of empirical data that the *trans* ethylenic coupling constant J of type aHC=CHb is generally larger than that of *cis* isomer,*4 it may be concluded that Ia (J=15.6 c.p.s.) is *trans* and Ib (J=11.4 c.p.s.) is *cis*. While, Curtin, *et al.*[2] have observed that the vinylproton occurs at a higher field for *cis*- than *trans*-stilbene in nuclear magnetic resonance spectra. It was also described[3] that the signals of the vinylprotons in *cis*- and *trans*-stilbene were located at τ 3.43 and at τ 2.90 respectively.

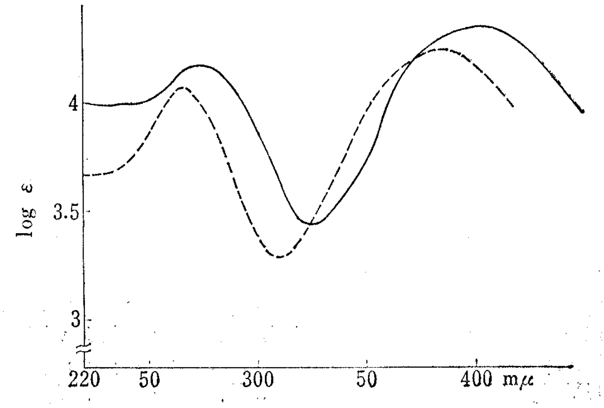

Fig. 3. Ultraviolet Absorption Spectra (in EtOH) of
——— *trans*-1-(5-Nitro-2-furyl)-2-methylthioethylene
------ *cis*-1-(5-Nitro-2-furyl-2-methylthioethylene

In *trans* isomer each proton lies in the plane of the two phenyl groups and is therefore deshielded, whereas, in *cis* isomer, the aromatic rings are titled and the deshielding of the olefinic protons is therefore reduced.[4]

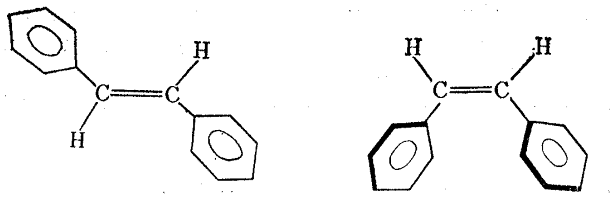

Fig. 4.

From the fact that the signal of one olefinic proton adjacent to 5-nitrofuran ring of Ib appeared at higher field (τ 3.31) than that of Ia (τ 2.70), it may be anticipated that 5-nitrofuran ring of Ib is displaced somewhat out of co-planarity with its vinylgroup.

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*4 In the literature[4] p. 85, it is described that the coupling constants for simple acyclic olefins usually lie well within the following ranges: *cis*- (J: 6~14 c.p.s.), *trans*- (J: 11~18 c.p.s.).

2) D.Y. Curtin, H. Gruen, B.A. Shoulders: Chem. & Ind. (London), **1958**, 1205.

3) N.S. Bhacca, L.F. Johnson, J.N. Schoolery: "NMR Spectra Catalog," **1** (1962), Varian Associates.

4) L.M. Jackman: "Application Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 126 (1959), Pergamon Press, London.

The ultraviolet absorption spectrum of Ia in ethanol showed an absorption at 272 mμ (ε 14340) and 404 mμ (ε 20620) and that of Ib at 266.5 mμ (ε 11340), 385 mμ (ε 15720) as illustrated in Fig. 3. It is well known that the *cis* isomer in olefin type aHC=CHc, where the substituents a and c may enter into resonance interaction with the olefinic system, has its absorption maximum at a slightly shorter wavelength and that its intensity is in all cases considerably weaker than that of the *trans* isomer. These absorption properties of Ia and Ib also provided a strong support for the suggestion of nuclear magnetic resonance.

From these data it is concluded that Ia is *trans*- and Ib is *cis*-1-(5-nitro-2-furyl)-2-methylthioethylene. The report concerning analogous compounds will be published in future.

Finally, fungistatic and bacteriostatic concentrations of Ia and Ib against the growth of *Trichophyton mentagrophytes*, *Tri. rubrum*, *Microsporum gypseum*, *Candida albicans* 57, *Aspergillus terreus*, and *Cryptococcus neoformens* on Sabouraud agar (pH 6) at 25° for 7 days and against that of *Staphylococcus aureus* 209P, *Escherichia coli* NIHJ, *Micrococcus lutenus*, *Bacillus subtilis*, *Klebsilla pneumonia*, and *Salmonella typhymurium* on bouillon agar (pH 7) at 37° for 3 days were shown in Table I respectively. A remarkable difference between Ia and Ib in their antifungal and antibacterial activities was not observed.

Table I. Antibacterial Actions of *trans*-1-(5-Nitro-2-furyl)-2-methylthioethylene (Ia) and *cis*-1-(5-Nitro-2-furyl)-2-methylthioethylene (Ib) (γ/ml.)

	Tri. men.	*Tri. rub.*	*Mic. gyp.*	*Can. alb.*	*Asp. ter.*	*Cry. neo.*	*Sta. aur.*	*Mic. lut.*	*Bac. sub.*	*Pro. vul.*	*Esc. col.*	*Kle. pne.*	*Sal. typ.*
Ia	5	5	5	20	10	20	50	50	50	50~20	20	5~2	10
Ib	5	5	5	10	10	20	50	50	20	20	20	5~2	5

Experimental[*5]

***trans*-1-(5-Nitro-2-furyl)-2-methylthioethylene (Ia)**——When solution of I in a little volume of CS_2 was allowed to stand overnight at room temperature in an open vessel, yellowish brown slender needles (Ia) appeared with reddish brown crystalline product. After CS_2 was removed completely under reduced pressure at room temperature, Ia being accompanied with very small amounts of Ib was separated mechanically. Recrystallization of crude Ia from CS_2 gave pure Ia as yellowish brown slender needles, m.p. 75.5°, UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 404 (4.31), 272 (4.16), $\lambda_{\min}^{\text{EtOH}}$ 322 mμ (3.41). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1503 (nitro), 1358 (nitro). *Anal.* Calcd. for $C_7H_7O_3NS$: C, 45.41; H, 3.81; N, 7.57; S, 17.28. Found: C, 45.58; H, 4.04; N, 7.30; S, 17.03.

***cis*-1-(5-Nitro-2-furyl)-2-methylthioethylene (Ib)**——Aforementioned reddish brown product with a few pieces of broken crystal of Ia was chromatographed on Al_2O_3 (neutral) with petr. ether-AcOEt (20:1). Very small amounts of a new substance having higher melting point than Ia was obtained from early eluted fractions. The next fractions were the mixture of the substance and Ia, from which Ia was removed mechanically again by such treatment with CS_2 as above-mentioned. Chromatography and recrystallization were repeated several times. Recrystallization of the combined new substance from CCl_4 gave pure Ib as pale yellow plate, m.p. 86~86.5°. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 385 (4.20), 266.5 (4.05), $\lambda_{\min}^{\text{EtOH}}$ 309 mμ (3.26). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1506 (nitro), 1350 (nitro). *Anal.* Calcd. for $C_7H_7O_3NS$: C, 45.41; H, 3.81; N, 7.57; S, 17.28. Found: C, 45.73; H, 3.85; N, 7.32; S, 17.25.

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[*5] Melting points are uncorrected.