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Nitration of Thenyl Derivatives. II. Preparation of Three Isomeric Mononitro Derivatives of 2-Thenyl Chloride and 2-Thenyl Acetate[*1]

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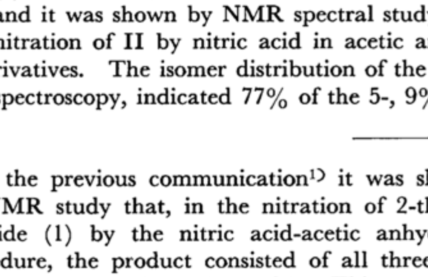
In connection with the investigation of the products of the nitration of 2-thenyl chloride (I) and 2-thenyl acetate (II), three isomeric mononitro derivatives of I and II were prepared, and it was shown by NMR spectral study that, as in the case of I, the product obtained in the nitration of II by nitric acid in acetic anhydride consisted of all three isomeric mononitro derivatives. The isomer distribution of the mononitro derivatives of II, as determined by infrared spectroscopy, indicated 77% of the 5-, 9% of the 4-, and 14% of the 3-nitro isomer.

In the previous communication[1] it was shown by NMR study that, in the nitration of 2-thenyl chloride (1) by the nitric acid-acetic anhydride procedure, the product consisted of all three isomeric mononitro derivatives of I. This seems to have been the first observation of the formation of the 4-substituted isomer in the electrophilic substitution of thiophene derivatives with an *o*-, *p*-directing group in the 2-position, though it had long been recognized that the substitution occurred predominantly at the 5-position and occurred at the 3-position, if at all, to only a minor extent. However, several attempts at the isolation of the isomers from the total product were all unsuccessful.



I: X=Cl III: X=Cl

II: X=OCOCH$_3$ VI: X=OCOCH$_3$

IV: X=Cl V: X=Cl

VII: X=OCOCH$_3$ VIII: X=OCOCH$_3$

The same is the case in the nitration of 2-thenyl acetate (II). Figure 1 shows the NMR spectrum of the nitration product[2] of II. The assignment of the peaks to each of the isomers is based on the ring-coupling constants[3] and on the coupling constants[4] between the methylene protons and the ring protons. The set of four strong peaks, two triplets at 5.59 ppm relative to cyclohexane as an internal standard and a doublet at 6.29 ppm (J=4.0 cps, $J_{2CH_2\text{-ring H}}=0.7$ cps), is clearly due to 5-nitro-2-thenyl acetate (VI), while the two doublets at 5.81 ppm and 6.10 ppm (J=5.8 cps) are due to 3-nitro-2-thenyl acetate (VII). The doublet at the lowest field is due to the proton at the 5-position of 4-nitro-2-thenyl acetate (VIII), while the proton at the 3-position appears as a quintet with a relative intensity of 1 : 2 : 2 : 2 : 1 centered at 6.13 ppm; the proton at the 3-position is coupled with both the one at the 5-position and the methylene protons at the 2-position to form two triplets, the overlapping of which shows a quintet ($J_{3\text{-}5}=1.6$ cps, $J_{2CH_2\text{-}3}=0.7$ cps). Besides the peaks arising from the ring protons, there are four peaks in the higher field which are related to the methylene and the methyl protons, the shifts of these peaks being 4.16 ppm (VII CH$_2$), 3.76 ppm (VI CH$_2$, VIII CH$_2$), 0.72 ppm (VII CH$_3$), and 0.66 ppm (VI CH$_3$, VIII CH$_3$) respectively. The chemical shifts and the coupling constants are in accordance with those expected for the spectra of VI, VII, and VIII.

In order to confirm the facts shown by the NMR spectra, two sets of three isomeric mononitro derivatives of I and II were prepared.

VI was isolated as colorless needles, mp 36—37°C, from the nitration product of II. The acidic hydrolysis of VI gave the corresponding alcohol, IX, which was then converted into III, bp 112—114°C/4 mmHg, by being treated with a mixture of zinc chloride and hydrochloric acid.

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1) Part I of this series: T. Sone and Y. Matsuki, This Bulletin, **37**, 1235 (1964).

2) T. Sone, K. Takahashi and Y. Matsuki, *ibid.*, **35**, 1420 (1962).

3) S. Gronowitz, "Advances in Heterocyclic Chemistry," Vol. 1, ed. by A. R. Katritzky, Academic Press, New York (1963), p. 7.

4) K. Takahashi, T. Sone, Y. Matsuki and G. Hazato, This Bulletin, **36**, 108 (1963).

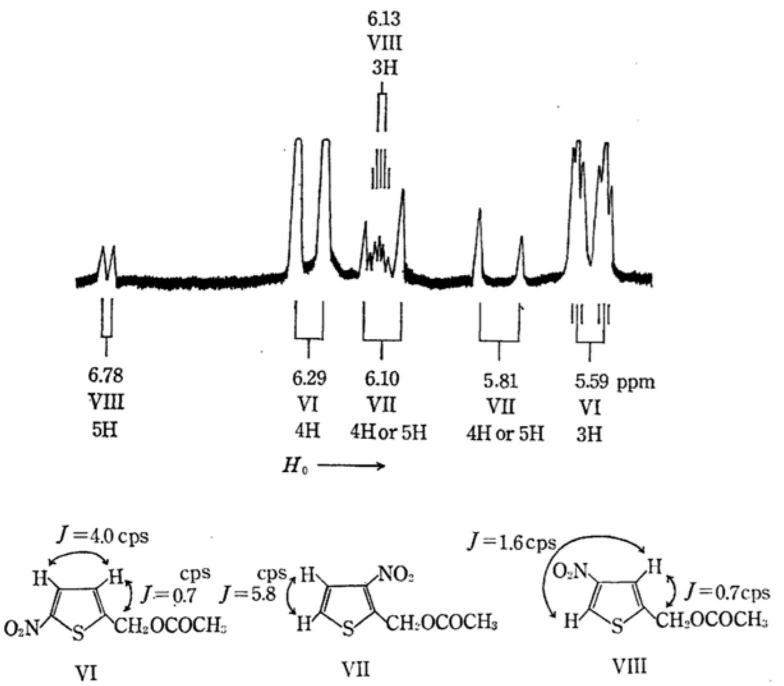
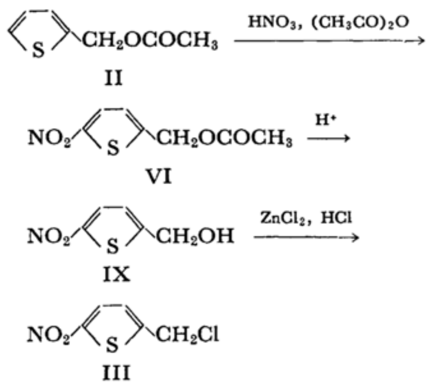
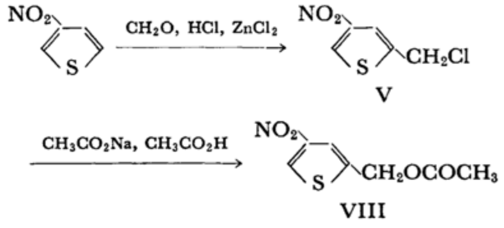
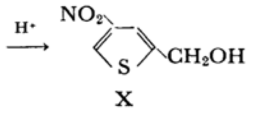


Fig. 1. NMR spectrum of the ring protons of the nitration product of 2-thenyl acetate (II) in carbon tetrachloride (60 Mc; Relative to cyclohexane as 0.00 ppm)

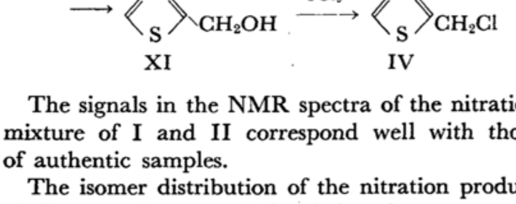


While 2-nitrothiophene, as well as nitrobenzene, is extremely difficult to be chloromethylated in the usual manner, 3-nitrothiophene is reactive enough for chloromethylation by a mixture of trioxane, hydrogen chloride, and zinc chloride; it gives V, bp 105—107°C/2 mmHg, which in turn is converted into VIII, mp 27—29°C.





VII,⁽⁶⁾ mp 60—61°C, was prepared by treating 3-nitro-2-thenyl bromide with sodium acetate in acetic anhydride. The hydrolysis of VII, followed by the chlorination of the resultant alcohol by phosphorus pentachloride, gave IV, mp 49—50°C.



The signals in the NMR spectra of the nitration mixture of I and II correspond well with those of authentic samples.

The isomer distribution of the nitration product of II was determined by infrared spectroscopy using the absorption bands at 814 cm^{-1} for VI, at 1077 cm^{-1} for VIII, and at 705 cm^{-1} for VII, indicating 77% of VI, 9% of VIII, and 14% of VII in the product. As the nitration was accompanied by the formation of a small amount of a resinous material, the results obtained by the determination of the isomer distribution should be considered with care, but they do clearly show that the 4-substitution occurs in a relatively higher proportion.

Experimental[5]

5-Nitro-2-thenyl Acetate (VI). 2-Thenyl acetate (31.2 g) was nitrated by nitric acid in acetic anhydride as has been described before[2] to give an oily mixture of nitro-2-thenyl acetates (25.2 g, 62.6%; bp 138—142°C/4 mmHg), a mixture which, on being left standing, partially solidified to colorless crystals. The crystals were collected by filtration and recrystallized from low-boiling petroleum ether to afford VI (9.0 g) as colorless needles, mp 36—37°C.

5-Nitro-2-thenyl Alcohol (IX). A mixture of VI (8.0 g) and 10% sulfuric acid (150 m*l*) was gently refluxed for 1 hr. The clear yellow solution was then cooled, and the resultant oily material was extracted with ether. The ether extract was dried (Na_2SO_4), and the ether was evaporated. The distillation of the residual oil gave IX (4.0 g, 63.0%) as a pale yellow oil, bp 148—150°C/3 mmHg, mp 20—21.5°C.

Found: C, 37.69; H, 2.71; N, 8.60%. Calcd for $C_5H_5NO_3S$: C, 37.73; H, 3.17; N, 8.80%.

5-Nitro-2-thenyl Chloride (III). A mixture of IX (5.0 g), zinc chloride (8.5 g), and hydrochloric acid (5.1 m*l*) was gently refluxed for 30 min, and then the reaction mixture was poured into water. The resultant oil was extracted with ether, and the ether extract was washed with water and dried (Na_2SO_4). After the evaporation of the solvent, the residue was distilled to give III (3.8 g, 68.2%) as a pale yellow oil, bp 112—114°C/4 mmHg, n_D^{20} 1.6213.

Found: C, 33.95; H, 2.08; N, 7.65%. Calcd for $C_5H_4ClNO_2S$: C, 33.81; H, 2.27; N, 7.88%.

3-Nitro-2-thenyl Alcohol (XI). A mixture of VII[6] (10 g) and 10% sulfuric acid (180 m*l*) was gently refluxed for 1 hr. The solution was then decolorized with charcoal and cooled to yield pale yellow needles (5.5 g, mp 71—72°C). Another crop of XI (1.6 g, mp 71—72°C) was obtained by extracting the filtrate by ether and by the subsequent evaporation of the solvent. The total yield of XI was 7.1 g (89.9%). The recrystallization of the crude XI from water gave pale yellow needles, mp 71—72°C.

Found: C, 37.73; H, 2.99; N, 8.56%. Calcd for $C_5H_5NO_3S$: C, 37.73; H, 3.17; N, 8.80%.

3-Nitro-2-thenyl Chloride (IV). To a mixture of XI (3.2 g) and chloroform (30 m*l*), phosphorus pentachloride (4.2 g) was added in small portions with shaking at room temperatre. After standing overnight, the reaction mixture was washed with water and dried ($CaCl_2$). The evaporation of the solvent and the recrystallization of the crude crystalline product from a mixture of ether and petroleum ether gave IV (2.1 g, 59.1%) as pale yellow prisms, mp 49—50°C.

Found: C, 33.81; H, 2.27; N, 7.88%. Calcd for $C_5H_4ClNO_2S$: C, 33.90; H, 2.30; N, 7.76%.

4-Nitro-2-thenyl Chloride (V). Into a mixture of 3-nitrothiophene (6.5 g), trioxane (2.4 g), zinc chloride (2.6 g), and carbon tetrachloride (50 m*l*), a stream of dry hydrogen chloride was stirred for 30 min. Then the mixture was gradually warmed to 50°C and stirred for 1 hr at that temperature, while the stream of hydrogen chloride continued to pass through. The resultant solution was poured into water, and the organic layer was separated, washed well with water, dilute sodium carbonate solution, and again with water, and dried. After the solvent had been removed, the residue was distilled under reduced pressure to yield V as a pale yellow oil, along with a small amount of a high-boiling material which was not examined further. Yield 4.1 g (46.1%). Bp 105—107°C/2 mmHg, n_D^{20} 1.6065, d_4^{20} 1.4825.

Found: C, 33.89; H, 2.02; N, 7.52%. Calcd for $C_5H_4ClNO_2S$: C, 33.81; H, 2.27; N, 7.88%.

4-Nitro-2-thenyl Acetate (VIII). A mixture of V (4.6 g), anhydrous sodium acetate (3.5 g) and acetic anhydride (20 m*l*) was heated for 6 hr at 60—70°C, and then gently refluxed for 4 hr. The mixture was cooled and poured into water. The resulting organic layer was extracted with ether, and the ether extract was washed with water and dried (Na_2SO_4). After the evaporation of the solvent, the residue was distilledunder reduced pressure to give crude VIII (3.3 g; bp 120—135°C/2—3 mmHg), which was found to contain a small amount of the starting chloride. The above distillate was then gently boiled for 5 hr with anhydrous sodium acetate (1 g) in acetic anhydride (5 m*l*), after which the reaction mixture was treated as before. The distillation of the product gave VIII (2.0 g, 38.4%) as a pale yellow oil, bp 129—131°C/3.5 mmHg, mp 27—29°C.

Found: C, 41.44; H, 3.42; N, 7.22%. Calcd for $C_7H_7NO_4S$: C, 41.78; H, 3.50; N, 6.90%.

4-Nitro-2-thenyl Alcohol (X). VIII (0.8 g) was treated with dilute sulfuric acid in the same way as has been described for VI. Crude alcohol (0.4 g, 63.4%; mp 52—54°C) was recrystallized from a mixture of ether and petroleum ether to yield colorless needles, mp 54—55°C.

Found: C, 37.81; H, 2.96; N, 8.47%. Calcd for $C_5H_5NO_3S$: C, 37.73; H, 3.17; N, 8.80%.

IR Spectrophotometric Determination of the Isomer Distribution of Nitro-2-thenyl Acetates. The quantitative analysis was carried out by a routine peak-intensity method based on the proportionality between the concentration and the absorption-peak height. The calibration spectra for the pure nitro-2-thenyl acetates were measured in a 0.5-mm cell in carbon disulfide solutions, the absorption bands chosen as key bands for the determination being 814 cm^{-1} for VI, 1077 cm^{-1} for VIII, and 705 cm^{-1} for VII. A linear relationship exists between the concentration of the isomers and the optical density within the concentration range examined. Known mixtures prepared from pure samples of each isomer were analyzed in order to determine the accuracy, and the results

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[5] All melting points and boiling points are uncorrected. The infrared spectra were recorded with a Hitachi EPI-2A spectrophotometer. The NMR spectra were recorded with a Varian Associates Model V-4300B or A-60 spectrophotometer at 60 Mc, using cyclohexane as an internal reference. The microanalyses were carried out by Miss Yoko Endo and Miss Noriko Matsukawa of this Institute, to whom the authors are indebted.

[6] H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.*, **79**, 2556 (1957).

were examined by Youden's method[7] to reveal that the standard deviations were 0.80%, 0.67%, and 0.96% for VI, VIII, and VII respectively.

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7) W. J. Youden, *Anal. Chem.*, **19**, 946 (1947).