DIRECTIVE NATURE OF THE NITRATION OF THE OXIMES OF 2-ACETYLTHIOPHENE AND 2-PROPIONYLTHIOPHENE

B. P. Fabrichnyi, S. M. Kostrova,
G. P. Gromova, and Ya. L. Gol'dfarb

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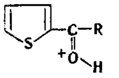
A method of obtaining pure 2-acetyl- and 2-propionyl-5-nitrothiophenes by nitrating the oximes of the corresponding ketones with the subsequent isolation from the mixtures formed of the pure oximes of the 2-acyl-5-nitrothiophenes and their saponification has been developed. The pure 2-acetyl- and 2-propionyl-4-nitrothiophenes have been isolated by crystallization from the products of the nitration of the corresponding ketones, which form in each case a mixture of the corresponding 2-acyl-4-nitro- and 2-acyl-5-nitrothiophenes containing about 90% of the 4-nitro isomer.

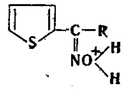
The nitration of 2-acetylthiophene leads to the formation of a mixture of 2-acetyl-4-nitro- and 2-acetyl-5-nitrothiophenes [1-3], and the influence of protonation on the composition of the mixture formed has been shown. According to this work [4, 5], the mixture formed by the action of potassium nitrate on a solution of 2-acetylthiophene in concentrated sulfuric acid contains about 90% of 2-acetyl-4-nitrothiophene.

When 2-propionylthiophene was nitrated, apparently only 4-nitro-2-propionylthiophene was isolated in the individual state and the quantitative composition of the mixture of isomeric nitro ketones was not determined [6, 7].

According to our results, the mixture of isomeric nitro ketones formed by the action of potassium nitrate on a solution of 2-propionylthiophene in sulfuric acid contains about 90% of 4-nitro-2-propionylthiophene. By crystallization of the mixtures of nitro ketones formed in the nitration of 2-acetyl- and 2-propionylthiophenes we have isolated the pure 2-acyl-4-nitrothiophenes.

2-Acyl-5-nitrothiophenes may prove to be suitable as intermediates for the synthesis of substances possessing an antibacterial action [6, 7]. Consequently, it was a matter of interest to find conditions for changing the direction of nitration in favor of the 2-acyl-5-nitrothiophenes. In our opinion, this result could be achieved by using for nitration not the alkyl 2-thienyl ketone but its oxime. In actual fact when the oxime is used the influence of the protonation effect must be considerably weaker than in the case of the ketone itself because an oxygen atom further from the thiophene ring undergoes protonation.





The nitration of the oximes of carbonyl compounds has been repeatedly used previously in the furan series [8, 9], but in all cases only the oximes of 2-acyl-5-nitrofurans were obtained. This result is not unexpected if one considers that the oxygen atom in the furan ring possesses a considerably weaker orienting influence than the sulfur atom in the thiophene ring. The nitration of oximes of 2-acylthiophenes has not been investigated previously.

Taking into account the opposite influences of the two factors (protonation and the orienting influence of the sulfur atom), it appeared quite likely that the nitration of the oximes of the 2-acylthiophenes would lead to an increased content of the 5-nitro isomers.

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The results of our experiments confirmed this assumption. The nitration of solutions of the oximes of 2-acetylthiophene and of 2-propionylthiophene* in sulfuric acid formed in each case a mixture of the oximes of the isomeric nitro ketones the saponification of which gave a mixture of nitro ketones containing, according to GLC, the 2-acyl-4-nitro- and 2-acyl-5-nitrothiophenes in a ratio of approximately 1 : 1. For the preparative production of a pure 2-acyl-5-nitrothiophene, potassium nitrate was added to a solution of the oxime in sulfuric acid, the reaction mixture was poured onto ice, the precipitate was filtered off, and the pure oxime of the 5-nitro ketone was isolated from the mixture of 2-acyl-4-nitro- and 2-acyl-5-nitrothiophenes by crystallization. The saponification of this oxime by boiling it with dilute sulfuric acid or hydrochloric acid gave the pure 5-nitro ketone.

EXPERIMENTAL

The amounts of 2-acyl-4-nitro- and 2-acyl-5-nitrothiophenes were determined in relation to known mixtures by the GLC method: LKhM-8M chromatograph with a flame-ionization detector, carrier gas nitrogen, rate of flow of gas 30 ml/min, temperature 200°C, stainless steel column 1.5 m long and 1.5 mm in diameter containing 10% of poly(ethylene adipate) on Chromosorb P (120-140 mesh).

Nitration of 2-Acetylthiophene. Nitration was performed under conditions close to those described elsewhere [4]. With water cooling, 8.27 g (0.06 mole) of 2-acetylthiophene was gradually added to 80 ml of 93% sulfuric acid and, with vigorous stirring at 0 to 5°C, 8.7 g (0.08 mole) of ground potassium nitrate was gradually added to the resulting orange solution. The solution was stirred for another 30 min at about 0°C and was then poured onto ice, and the precipitate was filtered off and washed with water until the wash waters no longer had an acid reaction to Congo Red. After drying, 10 g of a mixture of 2-acetylnitrothiophenes was obtained. The mother solution was extracted with chloroform. After the elimination of the solvent, 0.5 g of a mixture of nitro ketones remained which was added to the main product. The total yield of the mixture of 2-acetyl-4-nitro- and 2-acetyl-5-nitrothiophenes was 94%; mp 86-114°C. According to GLC, the mixture contained 85% of the 4-nitro isomer and 15% of the 5-nitro isomer.

Isolation of 2-Acetyl-4-nitrothiophene. A solution of 3.4 g of the mixture of 2-acetylnitrothiophenes in 34 ml of boiling ethanol was treated with activated carbon. The filtrate was left overnight at room temperature. The crystals that deposited were filtered off and washed with 5 ml of ethanol. The yield of practically pure 2-acetyl-4-nitrothiophene containing, according to GLC, only traces of 2-acetyl-5-nitrothiophene was 1.85 g (54% of the mixture of nitro ketones), mp 126-128°C. According to the literature [2], mp 126-127°C.

Nitration of 2-Propionylthiophene. Nitration was performed under the conditions used for the nitration of 2-acetylthiophene. The yield of the mixture of nitro ketones was 75%, mp 105-125°C. According to PMR spectroscopy and GLC, the mixture contained about 90% of 4-nitro- and 10% of 5-nitro-2-propionylthiophene. In addition, GLC showed the presence of a small amount of dinitrothiophene in the reaction product.

Isolation of 4-Nitro-2-propionylthiophene. A solution of 14.4 g of the mixture of nitro ketones in 100 ml of boiling acetone was treated with activated carbon. Water was added to the hot filtrate until crystallization began (60 ml), and then 10 ml of acetone was added and the mixture was left at room temperature. The precipitate was filtered off to give 8.2 g of a substance with mp 136-138°C which, on distillation, yielded 6.4 g (44.5% of the mixture of nitro ketones) of pure (according to GLC) 4-nitro-2-propionylthiophene with mp 138-139°C. According to the literature [6], mp 140-141°C. Oxime, mp 114-115°C. Found: N 14.0; 14.1%. $C_7H_8N_2O_3S$. Calculated: N 14.0%. On prolonged storage, the oxime decomposed with the liberation of oxides of nitrogen.

Oximation of 2-Acetylthiophene. A mixture of 39 g (0.56 mole) of hydroxylamine hydrochloride and 46 g (0.56 mole) of anhydrous sodium acetate in 133 ml of water, 167 ml of ethanol, and 44.7 g (0.35 mole) of 2-acetylthiophene was boiled for 5 h and then the solution was left overnight in the refrigerator, and the crystals were filtered off and washed with water. This gave 28.9 g of 2-acetylthiophene oxime with mp 110-114°C. According to the literature [10, 11]: mp 110°C, 112-113°C. Dilution of the mother solution yielded another 11.9 g of a mixture of isomeric oximes with mp 80-86°C. The two portions of oximes, with different proportions of the syn and anti isomers, were combined and used for nitration. The total yield was 82%.

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*On oximation, a mixture of syn and anti oximes is formed. The composition of this mixture depends on the reaction conditions.

Oximation of 2-Propionylthiophene. An oxime with mp 55-70°C was obtained by Krekeler's [12] method with a yield of 80%. According to the literature [13], mp 54-55°C. To obtain the previously undescribed high-melting 2-propionylthiophene oxime, a solution of 28 g (0.2 mole) of 2-propionylthiophene in 132 ml of ethanol was added to a solution of 24.6 g (0.35 mole) of hydroxylamine hydrochloride and 25 g (0.45 mole) of caustic potash in 74 ml of water, and the mixture was boiled for 6 h and was left overnight at room temperature. The potassium chloride was filtered off and the filtrate was left overnight at a temperature of about −20°C. The crystals were filtered off and repeatedly washed with water. Weight 7.1 g, mp 90-92°C. On recrystallization from 75 ml of ethanol, 5.9 g of an oxime with mp 92-93°C was obtained. Dilution of the mother solutions with water gave another 14.55 g of oxime with mp 50-60°C.

The nitration of the two oximes gave practically identical results in each case.

Nitration of 2-Acetylthiophene Oxime. With stirring and cooling (temperature of the mixture about 8°C), 8.8 g (0.063 mole) of 2-acetylthiophene oxime was dissolved in 188 ml of 98% sulfuric acid. With vigorous stirring and cooling (temperature of the mixture from 0 to 5°C), 14.2 g (0.14 mole) of ground potassium nitrate was added in portions to the orange solution. Stirring was continued for another 30 min, the orange solution was poured onto 1 kg of crushed ice, and the precipitate was filtered off, washed repeatedly with water, and dried. This gave 20.1 g (81%) of a mixture of the oximes of 2-acetyl-4-nitro and 2-acetyl-5-nitrothiophenes with mp 120-170°C. According to its PMR spectrum, the mixture contained about 40% of the oxime of the 4-nitro isomer and 60% of the oxime of the 5-nitro isomer. The saponification of 3 g of the mixture of oximes obtained by boiling it with 60 ml of dilute (1 : 1) hydrochloric acid gave 2.56 g of a mixture of nitro ketones containing, according to GLC, about 55% of 2-acetyl-5-nitro- and 45% of 2-acetyl-4-nitrothiophenes.

Isolation of Pure 2-Acetyl-5-nitrothiophene Oxime. A solution of 20.1 g of the mixture of oximes in 200 ml of hot ethanol was treated with activated carbon and the hot filtrate was treated gradually with 175 ml of water (until crystallization from the boiling solution began) and then with 20 ml of ethanol. The mixture was left overnight at room temperature. The yellow crystals were filtered off, washed with 50% ethanol (2 × 20 ml), and dried to give 10.0 g (50%, calculated on the mixture of oximes) of pure 2-acetyl-5-nitrothiophene oxime with mp 188-189°C. According to the literature [2], mp 189°C.

Isolation of 2-Acetyl-5-nitrothiophene. A mixture of 5.0 g of 2-acetyl-5-nitrothiophene oxime and 100 ml of dilute (1 : 3) hydrochloric acid was boiled for 3 h (part of the substance sublimed). After cooling, the crystals were filtered off, washed with water, and dried, giving 4.56 g of impure 2-acetyl-5-nitrothiophene with mp 99-104°C. This was dissolved in 40 ml of boiling ethanol, and the solution was treated with activated carbon. Water was added to the hot filtrate until crystallization began (30 ml), and then the mixture was cooled to room temperature and the crystals were filtered off and washed with 10 ml of 50% ethanol, giving 3.5 g of 2-acetyl-5-nitrothiophene with mp 107-108°C. According to the literature [2], mp 107°C. When the mother solution was left to stand in the refrigerator, it deposited another 0.3 g of 2-acetyl-5-nitrothiophene with mp 107-108°C. The total yield of 2-acetyl-5-nitrothiophene was 83%. According to GLC, the products contained no 2-acetyl-4-nitrothiophene.

In another case, 5.0 g of 2-acetyl-5-nitrothiophene oxime was saponified by being boiled with dilute hydrochloric acid as described above, and the nitro ketone was distilled off with steam (about 1 liter of water distilled over). The crystals were filtered off and were dried, giving 3.85 g (yield 84%) of 2-acetyl-5-nitrothiophene with mp 107-108°C.

Nitration of the 2-Propionylthiophene Oxime. Nitration with mp 55-70°C was performed under the conditions given for the preparation of the mixture of 2-acetylnitrothiophene oximes. The yield of the mixture of nitro-2-propionylthiophene oximes was more than 90%; mp 105-150°C. According to the results of elementary analysis, the reaction product contained the nitro-2-propionylthiophenes as impurity because of the partial saponification of the oximes.

The mixture nitro-2-propionylthiophenes obtained by the saponification of the nitration product followed by steam distillation of the nitro ketones had mp 80-118°C, and according to GLC, contained 4-nitro- and 5-nitro-2-propionylthiophenes in a ratio of ~ 1 : 1.

Isolation of 5-Nitro-2-propionylthiophene Oxime. The mixture of nitro-2-propionylthiophene oximes (16.7 g) was boiled with a mixture of 80 ml of heptane and 80 ml of toluene. The insoluble residue was filtered off from the hot solution and was washed with hot heptane. The weight of residue enriched in the 5-nitro isomer was 7.0 g; mp 153-168°C. It was dissolved in 80 ml of boiling ethanol, the solution was treated with activated carbon, and water was added to the boiling filtrate until crystallization began (50 ml) and then 10 ml of ethanol was added and the mixture was left overnight at room temperature. The resulting crystals were filtered off and washed with 50% ethanol to give 5.0 g (30%, calculated on the mixture of oximes) of 5-nitro-2-propionylthiophene with mp 163-165°C. Found: N 14.1; 14.0%. $C_7H_8N_2O_3S$. Calculated: N 14.0%.

The oxime was apparently a mixture of syn and anti isomers, since after a series of recrystallizations of this substance from ethanol an oxime with mp 178-179°C was obtained.

The saponification of 5.0 g of the oxime with mp 163-165°C by boiling it with dilute hydrochloric acid under the conditions given above yielded, after steam distillation, 4.2 g (91%) of 5-nitro-2-propionylthiophene free, according to GLC, from the 4-nitro isomer; mp 88-89.5°C. According to the literature [6, 7], mp 83-87, 75-80°C.

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