SYNTHESIS OF SOME NITROGEN DERIVATIVES OF THE THIOPHENE ANALOG OF CINCHOPHEN

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2-Nitro-5-(4-carboxy-2-quinolyl)thiophene was obtained by nitration of 5-(4-carboxy-2-quinolyl)thiophene. Data from microbiological tests of the nitro-substituted thiophene and its carboxyl-group derivatives are presented.

We have previously described nitrogen derivatives of the bithiophene analog of cinchophen [1]. Continuing our investigations in this area to seek new biologically active compounds, we obtained nitro derivative II by nitration of 5-(4-carboxy-2-quinolyl)thiophene (I) – the thiophene analog of cinchophen – with a mixture of nitric and sulfuric acids [3]. To prove the structure of II, we performed the alternative synthesis of this compound by the Doebner–Miller synthesis from 2-formyl-5-nitrothiophene [4], aniline, and pyruvic acid. The absence of a melting-point depression for a mixture of II and the nitro compound obtained by alternative synthesis and the identical character of their IR spectra make it possible to assign the 2-nitro-5-(4-carboxy-2-quinolyl)thiophene structure to II.

The nitration of 5-(4-carbethoxy-2-quinolyl)thiophene (III) gave 2-nitro-5-(4-carbethoxy-2-quinolyl)-thiophene (IV), which was identical to the ester obtained by esterification of II.

The information in the literature regarding the biological activity of some amides and N-substituted amides [5] compelled us to obtain amides V and VI and N-substituted amides VII and VIII from I and II. Microbiological tests of the synthesized compounds in vitro demonstrated the antimicrobial activity with respect to *St. aureus*, *Bac. mesentericus* (II), *St. aureus*, *Bac. mesentericus*, *Sh. Sonnei*, *Bac. pyocyaneum* (IV), and *Bac. mesentericus* (VI). The other compounds proved to be inactive. The antimicrobial properties of the substances were studied by T. B. Ryskina at a standard preparation concentration of 400 μg /ml.

EXPERIMENTAL

N-(5-Nitro-2-thenylidene)aniline. A 1.9-g (0.02 mole) sample of freshly distilled aniline was added to 2.5 g (0.02 mole) of 2-formyl-5-nitrothiophene in 20 ml of ethanol, and the mixture was refluxed for 1 h. The resulting precipitate was removed by filtration and dried to give 4.1 g (88%) of a product with mp 104° (from alcohol). Found,%: C 57.2; H 3.5; S 13.7. $C_{11}H_8N_2O_2S$. Calculated,%: C 56.9; H 3.47; S 13.8.

2-Nitro-5-(4-carboxy-2-quinolyl)thiophene (II). A. A 10.2-g (0.04 mole) sample of I was added in portions to 75 ml of concentrated H_2SO_4 at 0°. After the solid had dissolved completely, the mixture was cooled to –3°, and a solution of 1.77 ml of concentrated HNO_3 (sp. gr. 1.51) in 25 ml of concentrated H_2SO_4 was added by drops in the course of 1 h. The mixture was then cooled and stirred for 2 h and poured carefully over ice to give 11.8 g (98%) of II with mp 292-293° (from alcohol). Found,%: C 55.8; H 2.6; S 10.6. $C_{14}H_8N_2O_4S$. Calculated,%: C 56.0; H 2.7; S 10.7.

B. A 6.38-g (0.07 mole) sample of pyruvic acid and three drops of concentrated H_2SO_4 were added successively dropwise to a cooled solution of 13.9 g (0.06 mole) of N-(5-nitro-2-thenylidene)aniline in 193 ml of glacial acetic acid. The mixture was heated on a boiling-water bath for 1 h, cooled, and diluted with water. The resulting precipitate was removed by filtration and dissolved in ammonium hydroxide. The ammonium hydroxide solution was neutralized with 10% hydrochloric acid, and the precipitate was washed with water and dried to give 5 g (28%) of a product with mp 292-293° (from alcohol).

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2-Nitro-5-(4-carbethoxy-2-quinolyl)thiophene (IV). A. Anhydrous gaseous hydrogen chloride was bubbled into a solution of 1.7 g (5.3 mmole) of II in 100 ml of ethanol for 2 h, after which the mixture was refluxed for 4 h, cooled, and diluted with water. The precipitated IV was removed by filtration, washed with water, and dried to give 1.7 g (98%) of a product with mp 171-172° (from alcohol). Found,%: C 58.4; H 3.7; S 9.9. $C_{16}H_{12}N_2O_4S$. Calculated,%: C 58.5; H 3.7; S 9.8.

B. The nitration of ester III under the conditions used for the synthesis of II (method A) gave IV with mp 171-172° (from alcohol) in 97% yield.

5-(4-Carboxamido-2-quinolyl)thiophene (V). A mixture of 2 g (7.9 mmole) of I and 17 ml of $SOCl_2$ was refluxed for 5 h. The excess $SOCl_2$ was removed in vacuo, and the residue was poured carefully into a mixture of NH_4OH and ice. The ice mixture was neutralized with 10% hydrochloric acid, and the amide was removed by filtration to give 1.33 g (66%) of a product with mp 238-239° (from dimethylformamide–water). Found,%: C 66.0; H 3.9; S 12.8. $C_{14}H_{10}N_2OS$. Calculated,%: C 66.1; H 4.0; S 12.7.

2-Nitro-5-(4-carboxamido-2-quinolyl)thiophene (VI) with mp 296-297° (from dimethylformamide–water) was similarly obtained in 75% yield. Found,%: C 56.4; H 3.0; S 10.5. $C_{14}H_{19}N_3O_3S$. Calculated,%: C 56.2; H 3.0; S 10.7.

5-(4-N-Phenylcarboxamido-2-quinolyl)thiophene (VII). An 8-ml sample of $SOCl_2$ was added to a suspension of 5 mmole of I in dry benzene, and the mixture was refluxed on a water bath for 1 h. The excess benzene and $SOCl_2$ were removed by distillation until a dry residue was obtained. The residue was washed with dry benzene, and 50 ml of benzene and a solution of 0.012 mole of aniline in 5 ml of benzene were added to the dry residue. The mixture was refluxed for 1 h, and the precipitate was removed by filtration, washed with water, and dried to give a product with mp 248° (from alcohol–acetone) in 90% yield. Found,%: C 72.5; H 4.2; S 9.6. $C_{20}H_{14}N_2OS$. Calculated,%: C 72.7; H 4.3; S 9.7.

2-Nitro-5-(4-N-phenylcarboxamido-2-quinolyl)thiophene (VIII). An 8-ml sample of $SOCl_2$ and three drops of dimethylformamide were added by drops to 5 mmole of II, and the mixture was refluxed for 4 h on a water bath. The mixture was then worked up as in the preparation of VIII to give a product with mp 322° (from dimethylformamide–water) in 95% yield. Found,%: C 63.8; H 3.5; S 8.6. $C_{20}H_{13}N_3O_3S$. Calculated,%: C 64.0; H 3.5; S 8.5.

The IR spectra of KBr pellets of the compounds were measured by V. I. Pavskii with an IKS-14 spectrophotometer at 660-1800 cm^{-1}.

LITERATURE CITED

1. M. N. Zemtsova and A. E. Lipkin, Khim. Geterotsikl. Soedin., 770 (1972).
2. M. Hartmann and E. Wybert, Helv. Chim. Acta, 2, 60 (1919).
3. H. A. Burch, J. Med. Chem., 12, 535 (1969).
4. V. S. Egorova, V. N. Ivanova, and N. I. Putokhin, Zh. Obshch. Khim., 34, 4084 (1964).
5. W. D. Roll, J. Pharm. Sci., 59, 1834 (1970).