# INVESTIGATION OF SOME NITROGEN COMPOUNDS OF 2,2'-DITHIENYL

## IV.* SYNTHESIS OF THE DITHIENYL ANALOG OF CINCHOPHEN AND ITS DERIVATIVES

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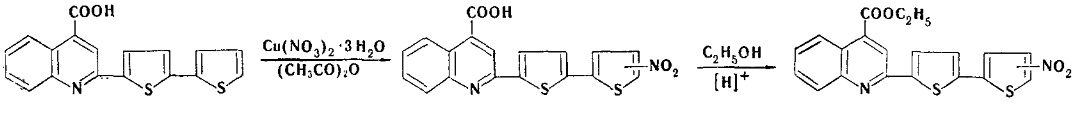
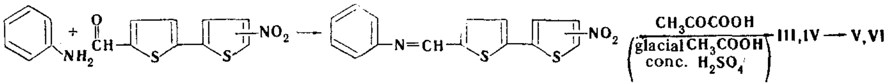
The dithienyl analog (I) of cinchophen was obtained by condensation of isatin with 5-acetyl-2,2'-dithienyl in alkaline media. The nitration of I with cupric nitrate in acetic anhydride gave 5-(4-carboxy-2-quinolyl)-5'-nitro and 5-(4-carboxy-2-quinolyl)-3'- nitro-2,2'-dithienyls, the structures of which were established by alternative synthesis.

Cinchophen [2] and some reported derivatives of cinchoninic acid [3] have antibacterial activity. We have synthesized the dithienyl analog (I) of cinchophen by a known method [4] by the condensation of isatin with 5-acetyl-2,2'-dithienyl. Two mononitro compounds were obtained by nitration of I with cupric nitrate in acetic anhydride [5]:



I III, IV V, VI

To prove the structures, we carried out the alternative preparation of these nitro compounds via the Doebner–Miller synthesis from the previously described [1] 5-formyl-5'-nitro- (VII) and 5-formyl-3'-nitro-2,2'-dithienyls (VIII):



VII, VIII IX, X

The absence of a depression of the melting points of mixtures of samples of the nitro compounds obtained by direct nitration and by alternative synthesis and the identical character of the IR spectra make it possible to assign the 5-(4-carboxy-2-quinolyl)-5'-nitro-2,2'-dithienyl and 5-(4-carboxy-2-quinolyl)-3'-nitro-2,2'-dithienyl structures to III and IV, respectively. Two mononitro compounds, which have structures V and VI, were obtained by nitration of the ethyl ester (II) of I with cupric nitrate in acetic anhydride.

Thus the same regularity of the orientation in the 5-substituted 2,2'-dithienyl molecule that was previously traced [6-8] is observed in the nitration of I and II.

The decarboxylation of III and IV in quinoline in the presence of copper powder gave 5-(2-quinolyl)-5'-nitro-2,2'-dithienyl (XI) and 5-(2-quinolyl)-3'-nitro-2,2'-dithienyl (XII). N-Substituted amides XIII-XXIV (see Table 1) were obtained by the reaction of the acid chlorides of acids I, III, and IV with aromatic amines.

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*See [1] for communication III.

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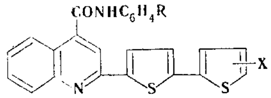
TABLE 1



| Compound | X | R | Mp, °C | Empirical formula | Found, % |  |  | Calc., % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | C | H | S | C | H | S |  |
| XIII | H | H | 309—310 | $C_{24}H_{16}N_2OS_2$ | 70,0 | 4,1 | 16,0 | 69,9 | 3,9 | 15,5 | 84 |
| XIV | H | $p$-CH$_3$ | 261—262 | $C_{25}H_{18}N_2OS_2$ | 71,0 | 4,0 | 15,3 | 70,4 | 4,2 | 15,0 | 69 |
| XV | H | $m$-CH$_3$ | 258—259 | $C_{25}H_{18}N_2OS_2$ | 70,4 | 4,5 | 15,0 | 70,4 | 4,2 | 15,0 | 76 |
| XVI | H | $o$-CH$_3$ | 236—237 | $C_{25}H_{18}N_2OS_2$ | 69,9 | 4,2 | 15,4 | 70,4 | 4,2 | 15,0 | 40 |
| XVII | 3'-NO$_2$ | H | 323—324 | $C_{24}H_{15}N_3O_3S_2$ | 62,9 | 3,7 | 13,6 | 63,0 | 3,3 | 14,0 | 49 |
| XVIII | 3'-NO$_2$ | $p$-CH$_3$ | 313 | $C_{25}H_{17}N_3O_3S_2$ | 63,4 | 3,9 | 13,3 | 68,7 | 3,6 | 13,6 | 77 |
| XIX | 3'-NO$_2$ | $m$-CH$_3$ | 310 | $C_{25}H_{17}N_3O_3S_2$ | 63,4 | 3,8 | 13,8 | 63,7 | 3,6 | 13,6 | 51 |
| XX | 3'-NO$_2$ | $o$-CH$_3$ | 267—268 | $C_{25}H_{17}N_3O_3S_2$ | 63,6 | 3,5 | 13,2 | 63,7 | 3,6 | 13,6 | 43 |
| XXI | 5'-NO$_2$ | H | 293—294 | $C_{24}H_{15}N_3O_3S_2$ | 62,9 | 3,2 | 13,9 | 63,0 | 3,3 | 14,0 | 87 |
| XXII | 5'-NO$_2$ | $p$-CH$_3$ | 298—299 | $C_{25}H_{17}N_3O_3S_2$ | 63,2 | 3,4 | 13,4 | 63,7 | 3,6 | 13,6 | 75 |
| XXIII | 5'-NO$_2$ | $m$-CH$_3$ | 282—283 | $C_{25}H_{17}N_3O_3S_2$ | 63,9 | 3,9 | 13,7 | 63,7 | 3,6 | 13,6 | 80 |
| XXIV | 5'-NO$_2$ | $o$-CH$_3$ | 304 | $C_{25}H_{17}N_3O_3S_2$ | 63,9 | 3,6 | 13,2 | 63,7 | 3,6 | 13,6 | 48 |

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*Compounds XIII-XVI were recrystallized from dimethylformamide—water, while XVII-XXIV were recrystallized from alcohol—acetone.

Microbiological tests of the synthesized compounds in vitro demonstrated that I and III have a certain antimicrobial activity with respect to Staphylococcus aureus and Bacillus mesentericus. The other compounds did not display antimicrobial activity with respect to St. aureus, Bac. mesentericus, E. coli, S. typti, Sh. flexneri, Sh. sonnei, and Bac. pyocyaneum. The antimicrobial properties of the preparations were studied by T. B. Ryskina using standard preparation concentrations of 400 μg/ml.

## EXPERIMENTAL

5-(4-Carbethoxy-2-quinolyl)-2,2'-dithienyl (II). Concentrated $H_2SO_4$ (3.4 ml) was added with cooling and stirring to 0.85 g (2.5 mmole) of I [4] in 26 ml of absolute alcohol, and the mixture was heated on a boiling-water bath for 6.5 h and neutralized with 10% $Na_2CO_3$. The precipitate was removed by filtration, washed with water, and dried to give 0.78 g (85%) of a product with mp 95-97° (from alcohol—acetone). IR spectrum: 1736 cm$^{-1}$ (carbethoxy group). Found: C 65.5; H 4.0; S 17.5%. $C_{20}H_{15}NO_2S_2$. Calculated: C 65.7; H 4.1; S 17.8%.

Nitration of 5-(4-Carboxy-2-quinolyl)-2,2'-dithienyl. A filtered (to remove copper salts) solution of diacetylorthonitric acid, obtained from 1.95 g (0.085 mole) of $Cu(NO_3)_2 \cdot 3H_2O$ and 10 ml of acetic anhydride, was added dropwise with stirring and cooling to 5° to 3.37 g (0.01 mole) of I in 85 ml of acetic anhydride, and the mixture was held at 8° for 2 h and then at room temperature for 2 h. The crystalline precipitate was removed by filtration, washed with water, and dried to give 2.47 g (65%) of III with mp 278-279° (from dioxane). Found: C 56.3; H 2.4; S 16.4%. $C_{18}H_{10}N_2O_4S_2$. Calculated: C 56.5; H 2.6; S 16.8%. The filtrate was poured into ice water, and the precipitate that formed after hydrolysis of the acetic anhydride was removed by filtration, washed with water, and dried to give 0.9 g (24%) of IV with mp 249.5-251° (from acetic acid). Found: C 56.3; H 2.5; S 16.6%. $C_{18}H_{10}N_2O_4S_2$. Calculated: C 56.5; H 2.6; S 16.8%.

Anil of 5-Formyl-5'-nitro-2,2'-dithienyl (IX). A 0.46-g (0.005 mole) sample of freshly distilled aniline was added to a solution of 1.2 g (0.005 mole) of 5-formyl-5'-nitro-2,2'-dithienyl in 200 ml of ethanol, and the mixture was refluxed for 3 h on a water bath. The precipitate was removed by filtration, washed with alcohol, and dried to give 1 g (61%) of a product with mp 153-154° (from alcohol). Found: S 26.5%. $C_{15}H_{10}N_2O_3S_2$. Calculated: S 26.8%.

The anil of 5-formyl-3'-nitro-2,2'-dithienyl (X) [1.23 g (74%)] was similarly obtained and had mp 161-162° (from alcohol). Found: S 26.4%. $C_{15}H_{10}N_2O_3S_2$. Calculated: S 26.8%.

5-(4-Carboxy-2-quinolyl)-5'-nitro-2,2'-dithienyl (III). A 0.3-g (4 mmole) sample of pyruvic acid was added dropwise with cooling to a solution of 1 g (3.1 mmole) of IX in 35 ml of glacial acetic acid, three drops of concentrated $H_2SO_4$ were added, and the mixture was heated on a boiling-water bath for 1 h, cooled, and diluted with water. The precipitate was removed by filtration and dissolved in ammonium hydroxide. The ammonium hydroxide solution was neutralized with 10% hydrochloric acid solution, and the precipitate was removed by filtration, washed with water, and dried to give 0.2 g (16%) of a product with mp 278° (from dioxane).

5-(4-Carboxy-2-quinolyl)-3'-nitro-2,2'-dithienyl (IV), 0.23 g (19%), with mp 249° (from glacial acetic acid) was similarly obtained.

5-(4-Carbethoxy-2-quinolyl)-5'-nitro-2,2'-dithienyl (V). A 0.2-g (0.49 mmole) sample of III was esterified by a method similar to that used to synthesize ester II to give 0.16 g (80%) of a product with mp 187° (from benzene). IR spectrum, $cm^{-1}$: 1734 (carbethoxy group), 1565, 1347 (nitro group). Found: C 58.6; H 3.3; S 15.2%. $C_{20}H_{14}N_2O_4S_2$. Calculated: C 58.8; H 3.5; S 15.6%.

Ester VI [0.15 g (75%)] with mp 159-160° (from alcohol) was similarly obtained. IR spectrum, $cm^{-1}$: 1732 (carbethoxy group), 1567, 1352 (nitro group). Found: C 58.5; H 3.3; S 15.5%. $C_{20}H_{14}N_2O_4S_2$. Calculated: C 58.8; H 3.5; S 15.6%.

5-(2-Quinolyl)-5'-nitro-2,2'-dithienyl (XI). A 2-g sample of copper powder was added to 1.91 g (0.005 mole) of V in 3 ml of quinoline, and the mixture was heated at 180° for 1.5 h and cooled. Hydrochloric acid (10%) was added, and the precipitate was removed by filtration, washed with 10% NaOH solution and water, and dried to give 1.1 g (65%) of a product with mp 225° (from alcohol–acetone). Found: S 18.7%. $C_{17}H_{10}N_2O_2S_2$. Calculated: S 18.8%.

5-(2-Quinolyl)-3'-nitro-2,2'-dithienyl (XII) [0.98 g (58%)] with mp 166-167° (from alcohol–acetone) was similarly obtained. Found: S 18.7%. $C_{17}H_{10}N_2O_2S_2$. Calculated: S 18.8%.

N-Arylamides XIII-XXIV (see Table 1). An 8-ml sample of $SOCl_2$ was added to a suspension of 0.005 mole of I, III, and IV in dry benzene, and the mixture was refluxed on a water bath for 1 h. The excess $SOCl_2$ was removed by distillation, the dry residue was washed with benzene, and 50 ml of benzene and a solution of 0.012 mole of the appropriate amine in 5 ml of benzene were added to it. The mixture was refluxed on a water bath for 1 h, and the solid was removed by filtration, washed with water, and dried.

The IR spectra of KBr pellets of the compounds were measured by V. I. Pavskii with an IKS-14 spectrophotometer.

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