## SOME NITROUS AND CARBONYL DERIVATIVES OF THE BITHIOPHENE ANALOG OF ATOPHAN

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The derivatives of 2-Ar-cinchoninic acid (I) described are biologically active substances. Thus atophan [1] has analgesic properties and is used in gout. The nitrofuran analog of atophan [2] is a known antibacterial agent against microorganisms such as <u>E. coli</u>, <u>Salmonella typhosa</u>, <u>Proteus vulgaris</u>, <u>Staphylococcus aureus</u>, <u>Streptococcus pyogenes</u>, and <u>Streptococcus agalactial</u>. A pyrrole analog of atophan has been described [3] which stimulates plant growth.

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We obtained the bithiophene analog of atophan (III) according to the method described in [4] by condensation of isatin with 5-acetyl-2,2'-dithienyl (II). The esterification of III yielded its methyl (IV) and ethyl (V) ester. The reactions proceeded by electrophylic substitution of II, VI, and V (nitration [5], acetylation [6], formylation according to Vilsmeier [7], and reactions of the acid chlorides of III, VI, and VII, yielding the N-substituted amides XIII-XXIV(Table 1).



The structure of VI and VII and of their ethyl esters IX and X were determined by back synthesis according to Doebner-Miller from the earlier described [8] 5-formyl-5'-nitro- and 5-formyl-3'-nitro-2,2'- dithienvls via the intermediate Schiff bases with aniline (XXV and XXVI).



The absence of an mp reduction in samples of a mixture of the nitro compounds obtained by direct and back synthesis and the identity of their IR spectra showed that in the compounds VI and IX the nitrogroup is located at position 5', and in VII and X at 3' of the bithiophene part of the molecule. The structure of XII was determined by using it for the synthesis of the compound described in [4], 5,5'-di-(4-carbomethoxy-2-quinolyl)-2,2'-dithienyl (XXVIII), according to Pfitsinger:



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TABLE 1. N-Substituted Amides

Com- pound	x	R	Yield (in %)	s C)	Calculated (in %)			Empirical	Found (in %)		
				Mp (i) degre	с	н	s	formula	с	н	S
XIII	н	C <sub>6</sub> H <sub>5</sub> NH	84,1	309	69,88	3,91	15,54	C <sub>24</sub> H <sub>16</sub> N <sub>2</sub> OS <sub>2</sub>	70,01	4,14	16,02
XIV	Н	n=CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH	69,2	261-	70,39	4,25	15,03	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> OS <sub>2</sub>	71,04	4,04	15,26
XV	н	M=CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH	76,1	258-	70,39	4,25	15,03	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> OS <sub>2</sub>	70,35	4,53	15,02
XVI	н	o=CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH	40,5	9 236 7	70,39	4,25	15,03	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> OS <sub>2</sub>	70,15	4,25	15,43
XVII	$3' = NO_2$	C <sub>6</sub> H₅NH	49,1	323-	63,04	3,32	14,01	C <sub>24</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	62,90	3,66	13,61
XVIII XIX XX	$3' = NO_2$ $3' = NO_2$ $3' = NO_2$	$n = CH_3C_6H_4NH$ $m = CH_3C_6H_4NH$ $o = CH_3C_6H_4NH$	77,5 51,5 43,0	313 310 267—	$\begin{array}{c} 63,67\\ 63,67\\ 63,67\\ 63,67\end{array}$	3,63 3,63 3,63	13,59 13,59 13,59	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub> C <sub>25</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub> C <sub>25</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	63,4 63,42 63,58	3,90 3,81 3,49	13,28 13,81 13,81
XXI	$5' = NO_2$	C <sub>6</sub> H <sub>5</sub> NH	86,7	293	63,04	3,32	14,01	$C_{24}H_{15}N_3O_3S_2$	63,89	3,17	13,91
XXII	$5' = NO_2$	n=CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH	75,3	298-	63,67	3,63	13,59	$C_{25}H_{17}N_3O_3S_2$	63,17	3,43	13,38
XXIII	$5' = NO_2$	m=CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH	80,5	9 282	63,67	3,63	13,59	C <sub>25</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	63,89	3,87	13,69
XXIV	$5' = NO_2$	o=CH <sub>3</sub> C <sub>6</sub> H₄NH	48,3	304	63,67	3,63	13,59	$C_{25}H_{12}N_3O_3S_2$	63,91	3,59	13,24

<u>Note</u>. The compounds XIII-XXVI were crystallized from a mixture of dimethyl formamide-water; XVIII-XXIV were crystallized from an alcohol-acetone mixture.



Fig. 1. IR spectra of a known sample of compound XXVIII (a) and the specimen obtained from XII (b).

The absence of a depression of the mp in a sample of a mixture of our compound XXVIII with the same known compound and their identical IR spectra (see Fig. 1) led us to assign to XII the structure of 5-(4-carbomethyoxy-2-quinoly)-5'-acety]-2,2'dithienvl.

The structures of VIII and XI were determined from the identity of the corresponding acids and their esters obtained by mild oxidation of XI and XII and subsequent esterification.

The identity of the two samples of the acid (XII) obtained from XI and XII, respectively, and that of the two samples of



the ester (XXX) obtained from the same starting materials were shown in each case by mixed melting points and the similarity of the IR spectra, permitting VIII and XI to be assigned the structures of 5-(4-carboxy-2-quinolyl)-5'-formyl-2,2'-dithienyl and 5-(4-carbomethoxy-2-quinolyl)-5'-formyl-2,2'-dithienyl. The compounds XI and XII were characterized by their semicarbazones and thiosemicarbazones (XXXI-XXXIV).

The antimicrobial activity of the compounds was tested in a dense nutrient medium with a standard concentration of 400  $\mu$ g/ml in agar. As test bacteria we used gram-positive (St. aureus and the potato bacillus) and also gram-negative species (E. coli, Salmonella typhi, Shigella flexneri and sonnei and Ps. pyocyanea). In Table 2, we present the antibacterial spectrum of the compounds which showed antiseptic properties. In none of the other compounds subjected to microbiological screening did we detect any antimicrobial activity.

## TABLE 2. The Spectrum of the AntimicrobialAction of Biologically Active Compounds

Com		Test bacteria								
pound	1	2	3	4	5	6	7			
VI VII XXXIII	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++		  +			-			

Legend: 1) Staphylococcus; 2) potato bacillus (B. mesentericus); 3) E. coli; 4) Salmonella typhosa; 5) Shigella flexneri; 7) Pseudomonas pyocyanea; + fullbactericidal action;  $\pm$  bacteriostatic effect; - no effect.

## EXPERIMENTAL

5-Acetyl-2,2'-dithienyl (II) was obtained according to the method in [9].

5-(4-Carboxy-2-quinolyl)-2,2'-dithienyl (III) was obtained according to the method in [4].

5-(4-Carbethoxy-2-quinolyl)-2,2'-dithienyl (V). To 0.85 g of III in 26 ml absolute alcohol, 3.4 ml of concentrated sulfuric acid was added under cooling and stirring. The mixture is heated in a water bath for 6.5 h, then neutralized with a 10% solution of sodium carbonate. Yield: 96%, mp 96-97°C (from a mixture of alcohol and acetone); Found, %: S 17.53. C<sub>20</sub>H<sub>15</sub>NO<sub>2</sub>S<sub>2</sub>. Calculated, %: S 17.80.

IV was obtained in the same way. Yield 97%, mp 96°C (from an alcohol-acetone mixture). Found, %: C 65.68; H 4.11; S 18.14.  $C_{19}H_{13}NO_2S_2$ . Calculated, %: C 65.73; H 4.14; S 18.24.

Nitration of 5-(4-Carboxy-2-quinolyl)-2,2'-dithienyl (III). To 3.37 g of III in 85 ml acetic anhydride was added, under mixing at 5°C, a solution of diacety lorthonitric acid obtained by mixing 1.95 g of Cu(NO<sub>3</sub>)<sub>2</sub> · 3H<sub>2</sub>O and 10 ml acetic anhydride and filtering off the copper salts. After introduction of the whole nitrating mixture, the reaction mass was left to stand for 2 h at 8°C and then for 2 h at room temperature. The crystalline precipitate was filtered off, washed with water and dried. Yield 64.6%, mp 278-279°C (from dioxane). Found, %: C 56.49; H 2.57; S 16.42. C<sub>18</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>. Calculated, %: C 56.53; H 2.63; S 16.79. The filtrate was poured into ice water (with ice); after hydrolysis of the acetic anhydride, the precipitate was filtered off, washed with water and dried. Yield, 23,6%; mp 249.5-251°C (from acetic acid). Found, %: C 56.45; H 2.61; S 16.62. C<sub>18</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>. Calculated, %: C 56.53; H 2.63; S 16.79.

 $\frac{5-(4-\text{Carbomethoxy-2-quinolyl})-5'-\text{formyl-2,2'-dithienyl (XI)}. To 10 \text{ ml of phosphorus oxychloride,} 25 \text{ ml of freshly distilled dimethylformamide was added under cooling in ice water and stirring. After 10 min, 5 g of finely ground IV was added in small portions. The mixture gradually acquired a red hue, turned darker and thicker. The reaction mixture was gradually heated to 70-80°C, continuing the stirring for another 3 h. When the mixture had considerably thickened 3-5 ml dimethylformamide was added. Then the reaction mixture was poured into cold water, thereby precipitating a dark brown sediment. The mixture was filtered off and air-dried. Yield, 92.5%, mp 187-188°C (from an alcohol-acetone mixture). Found, %: C 63.19; H 3.47; S 16.98. C<sub>20</sub>H<sub>13</sub>NO<sub>3</sub>S<sub>2</sub>. Calculated, %: C 63.30; H 3.45; S 16.90. Semicarbazone (XXXI): mp 250-251°C (from an alcohol-acetone mixture). Found, %: C 57.71; H 3.65; S 14.26. C<sub>21</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>. Calculated, %: C 57.71; H 3.65; S 14.26. C<sub>21</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>. Calculated, %: C 57.71; H 3.65; S 14.26. C<sub>21</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>. Calculated, %: C 57.78; H 3.69; S 14.66. Thiosemicarbazone (XXXII): mp 224-225°C (from an alcohol-acetone mixture). Found, %: C 56.63; H 3.89; S 20.53.$ 

 $\frac{5-(4-\text{Carboxy-2-quinolyl})-5'-\text{formyl-2,2'-dithienyl (VIII)}}{(\text{from an alcohol-acetone mixture}). Found, \%: C 62.31; H 2.97; S 17.32. C<sub>19</sub>H<sub>11</sub>NO<sub>3</sub>S<sub>2</sub>. Calculated, \%: C 62.45; H 3.04; S 17.55.$ 

5-(4-Carbomethoxy-2-quinoly)-5'-acetyl-2,2'-dithienyl (XII). 9.5 g of phosphorus pentoxide was mixed with 5.5 ml of 90% orthophosphoric acid under cooling in ice water, gradually heated to 80-85°C, and stirring was continued for another 1-1,5 h at the same temperature. The prepared polyphosphoric

acid was cooled to 20°C, and 1 ml acetic anhydride was added. The next addition under stirring was 2 g of powdered IV. This addition raised the temperature to 34°C. When the mixture had considerably thickened 2-3 ml of glacial acetic acid was added. The reaction flask was heated to 50°C, and this temperature was maintained under continuous stirring for another 3.5 h. The hot mixture was then poured on ice, neutralized with a 10% solution of sodium carbonate until the medium turned weakly acid, and left to stand overnight. The brown sediment was filtered off and air-dried. Yield 50%, mp 210°C (from an alcohol- acetone mixture). Found, %: C 63.95; H 3.75; S 16.37.  $C_{21}H_{15}NO_3S_2$ . Calculated, %: C 64.08; H 3.82; S 16.30. Semicarbazone (XXXIII): mp 253-254°C (from an alcohol- acetone mixture). Found, %: C 58.48; H 3.98; S 14.32.  $C_{22}H_{18}N_4O_3S_2$ . Calculated, %: C 58.65; H 4.03; S 14.23. Thiosemicarbazone (XXXIV): mp 237-238°C (from an alcohol- acetone mixture). Found, %: C 56.61; H 3.87; S 20.55.  $C_{22}H_{18}N_4O_2S_3$ . Calculated, %: C 56.63; H 3.89; S 20.58.

The Schiff Base XXV. To a solution of 1.2 g of 5-formyl-5'-nitro-2,2'-dithienyl in 200 ml alcohol, 0.46 g of freshly distilled aniline was added. The mixture was boiled for 3 h in a water bath. The sediment was filtered off, washed with alcohol and dried. Yield 60.6%, mp 153-154°C (from alcohol). Found, %: C 54.43; H 3.02; S 19.22.  $C_{15}H_{10}N_2O_3S_2$ . Calculated, %: C 54.53; H 3.05; S 19.41.

<u>The Schiff Base XXVI.</u> This is obtained in the same way as XXV. Yield 74.4%, mp 161-162°C (from alcohol). Found, %: C 54.37; H 2.98; S 19.31.  $C_{15}H_{10}N_2O_3S_2$ . Calculated, %: C 54.53; H 3.05; S 19.41.

5-(4-Carboxy-2-quinolyl)-5'-nitro-2,2-dithienyl (VI). A portion of XXV (1 g) was dissolved in 35 ml of glacial acetic acid; 0.3 g pyruvic acid was added by drops under cooling and then 3 drops of concentrated sulfuric acid. The mixture was heated in a water bath for 1 h, then cooled and diluted with water. The precipitate was filtered off and dissolved in ammonia. The ammoniacal solution was neutralized with 10% hydrochloric acid, the precipitate was filtered off, washed with water and dried. Yield 16.3%, mp 278°C (from dioxane).

<u>5-(Carboxy-2-quinolyl)-3'-nitro-2,2'-dithienyl (VII).</u> Obtained like VI. Yield 18.8%, mp 249°C (from glacial acetic acid).

 $\frac{5-(4-\text{Carbethoxy-2-quinolyl})-5'-\text{nitro-2,2'-dithienyl (IX).}}{\text{Carbethoxy-2-quinolyl}-5'-\text{nitro-2,2'-dithienyl (IX).}} A portion of VI (0.21 g) was esterified by the same method as for V. Yield 80.0%, mp 187°C (from benzene). Found, %: C 58.27; H 3.44; S 15.17. C<sub>20</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>. Calculated, %: C 58.52; H 3.43; S 15.62.$ 

 $\frac{5-(4-\text{Carbethoxy-2-quinolyl})-3'-\text{nitro-2,2'-dithienyl (X)}}{\text{Yield 75\%, mp 159-160°C (from alcohol).}}$  This was obtained in the same way as IX.

 $\frac{5-(4-\text{Carbomethoxy-2-quinolyl})-5'-(4-\text{carboxy-2-quinolyl})-2,2'-\text{dithienyl} (XXVII).}{9 \text{ XII, } 0.6 \text{ g isatin, } 2.3 \text{ ml of a } 28\%} \text{ aqueous potassium hydroxide solution, and } 60 \text{ ml alcohol was heated under reflux and filtered.} The cooled filtrate was acidified with dilute acetic acid. The amorphous, claret red sediment was freed by hot water of the excess isatin. Yield 73.5\%, mp 297-305° (from dioxane).}$ 

5,5'-Di-(4-carbomethoxy-2-quinolyl)-2,2'-dithienyl (XXVIII). This was obtained by the method used for V. The reaction continued for 12 h. Yield 10%, mp 269-271°C (from a 1:1 mixture of dioxane-ace-tone).

The acid of XXIX was obtained like the earlier-described acid of XI. It was used for the synthesis of the methyl ester XXX in the way described for V; mp 145-147°C (from an alcohol-acetone mixture). Found, %: C 59.89; H 3.59; S 15.82%. C<sub>21</sub>H<sub>15</sub>NO<sub>4</sub>S<sub>2</sub>. Calculated, %: C 60.03; H 3.64; S 15.66%.

N-Substituted Amides (XIII-XXIV). Thionyl chloride (8 ml) is added to a suspension of, respectively, 0.005 moles III, VI, and VII in dry benzene. The mixture is boiled on a water bath for 1 h, and the excess of benzene and thionyl chloride is distilled off to dryness. The residue is washed with benzene, 50 ml benzene is then added, and the solution of the corresponding amine (0.012 moles) in 5 ml benzene. The mixture is boiled over a water bath for 1 h, and the precipitate is filtered off, washed with water, and dried. The characteristics of the compounds XIII-XXIV obtained are presented in Table 1.

IR spectra were measured by V. I. Pavskii on an IKS-14 spectrophotometer in the 1800-660 cm<sup>-1</sup> region in potassium bromide pellets.

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