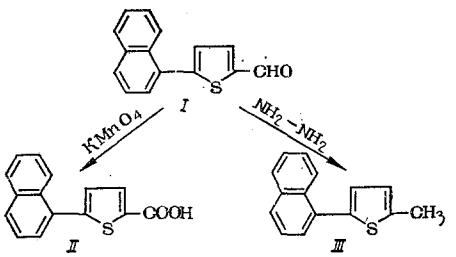
SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CERTAIN 2-(1-NAPHTHYL)-THIOPHENE DERIVATIVES

N. V. Stulin, A. E. Lipkin,
D. A. Kulikova, and É. A. Rudzim

UDC 615.281:547.73

It is known from the literature [1-4] that compounds containing thiophene rings frequently possess antimicrobial properties. In the quest for new, highly effective bacterial preparations in the thiophene series we synthesized for the first time 5-formyl-2-(1-naphthyl)-thiophene (I) and 2-(1-naphthyl)-5-thiophenecarboxylic acid (II) and studied their antimicrobial effect.

2-(1-Naphthyl)-thiophene, necessary for the synthesis, was obtained by the method of [5]. Its formylation with dimethylformamide in the presence of phosphorus oxychloride gave aldehyde (I), the oxidation of which yielded acid (II), while Kizhner reduction gave 5-methyl-2-(1-naphthyl)-thiophene (III).

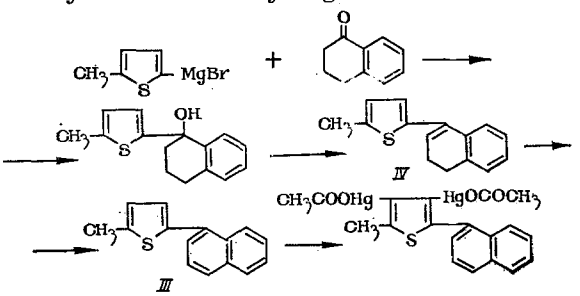


To confirm the structure of the synthesized compounds their IR spectra were measured. A band is observed in the IR spectrum of (I) in the region of 1664 cm^{-1}, which should be assigned to carbonyl stretching vibrations. The carboxyl in (II) gives a band in the region of 1685 cm^{-1}. The methyl group in (III) appears in the regions of 1390, 1480, and 2900 cm^{-1}.

The position of the CHO group in (I) was established by its transformation to compound (III), which is easily mercurated, going to the diacetoxymercury derivative having mp 214-217 deg (dec.).

Substitution of two, and not three, hydrogen atoms by the $HgOCOCH_3$ group makes it possible for us to propose that formylation of 2-(1-naphthyl)-thiophene occurred in position 5 of the thiophene ring.

The structure of (III) was confirmed by its synthesis from 5-methyl-2-thienylmagnesium bromide and α-tetralone with subsequent dehydration and dehydrogenation of intermediate reaction products by the scheme:



V. V. Kuibyshev Polytechnic Institute. Scientific-Research Institute of Biological Testing of Chemical Compounds, Kupavna, Moscow Region. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 9, No. 11, pp. 20-23, November, 1975. Original article submitted September 26, 1974.

TABLE 1. Minimum Concentrations Depressing Growth of Microorganisms (μg/ml)

Stimulator	Compound	
	I	II
Staphylococcus 209-R	12.5	12.5
Streptococcus 295	>100	>100
Pneumococcus type I	31.5	31.5
Diphtheria bacillus R-8	6.25	12.5
Anthracoid bacillus 1312	6.25	6.25
Escherichia coli 675	>100	>100
Bacillus pyocyaneus 165	>100	>100
Salmonella typhosa 1196	>100	>100
Dysentery bacillus 2a-516	>100	>100
Proteus vulgaris 5-26-III	>100	>100
Candidiasis inducer	20.9	500
Trichophytosis inducer	3.9	7.8
Microscorosis inducer	7.8	7.8
Tuberculosis bacillus in medium:		
without serum	6.25	11.5
with serum	100	200

Compound (III) is easily mercurated, giving 3,4-diacetoxymercuri-5-methyl-2-(1-naphthyl)-thiophene.

The identity of both samples of compound (III) was confirmed by elemental analysis data, IR spectra, and the absence of a melting point depression of a mixed sample of diacetoxymercury derivatives obtained from these samples.

The antimicrobial activity in a test tube was studied by the method of two consecutive cultures on a liquid culture medium. Testing was carried out on a spectrum of 14 strains, including five forms of Gram-positive bacteria (staphylococcus, streptococcus, pneumococcus, diptheria bacillus, anthracoid), five forms of Gram-negative bacilli (Escherichia coli, Bacillus pyocyaneus, Salmonella typhosa, dysenteric, proteus), three forms of pathogenic fungi (inducers of candidiasis, trichophytosis and microscorosis), and also tubercular bacillus of the human type ("Akademiya" strain). Experiments were carried out on a Sutton medium with the latter stimulant (without protein or with addition of 10% horse serum), on Hottinger bouillon with other bacteria, and on Subbarow medium with other fungi. The report of methods presented in the handbook [6] was followed in detail.

Results of investigations are presented in Table 1, from which it is seen that preparations (I) and (II) possess moderate (and approximately identically expressed) activity in relation to Gram-positive bacteria: Minimum bacteriostatic concentrations vary in the range of from 6 to 30 μg/ml for four of the five studied strains (streptococcus is insensitive). Both compounds do not depress growth of Gram-negative bacilli in concentrations of 100 μg/ml and less.

Both materials are highly active in relation to dermatophyte fungi: Minimal mycostatic concentrations are 4-8 μg/ml. The candidiasis inducer was found to be sensitive to compound (I) but not to compound (II). Moderate tuberculostatic effect of both compounds displayed in a medium without protein was virtually completely removed upon addition of serum.

The further synthesis of new derivatives of compounds (I) and (II) is of interest for the purpose of searching for effective chemotherapeutic preparations.

EXPERIMENTAL

IR spectra were measured on an IKS-14 spectrophotometer with an NaCl prism in KBr pellets in the region of 3000-690 cm^{-1}.

5-Formyl-2-(1-naphthyl)-thiophene (I). To a mixture of 12.6 g of 2-(1-naphthyl)-thiophene and 5.5 g of dimethylformamide gradually was added 10.8 g of phosphorus oxychloride; the mixture was heated on a water bath until liberation of hydrogen chloride ceased and was neutralized with a sodium bicarbonate solution. Unreacted product was steam-distilled. Yield 85%, mp 72-73 deg (from an ethanol–benzene

mixture). Found, %: C 75.33; H 4.34. $C_{15}H_{10}OS$. Calc., %: C 75.60; H 4.26. Semicarbazone: mp 198-199° (from ethanol). Found, %: C 65.07; H 4.60; N 13.96. $C_{16}H_{13}N_3OS$. Calc., %: C 65.06; H 4.43; N 14.22.

5-Methyl-2-(1-naphthyl)-thiophene (III). A mixture of 3.5 g of (I) and 4 ml of hydrazine hydrate in 15 ml of ethylene glycol was boiled for 10 min, 4 g of powdery potassium hydroxide was added, and the mixture was heated until liberation of nitrogen ceased. The oily layer was extracted with ether and dried with sodium sulfate. The ether was distilled and the residue was distilled in vacuum. Yield 33%, bp 171-175° (4 mm). Found, %: C 80.01; H 5.40; S 14.32. $C_{15}H_{12}S$. Calc., %: C 80.31; H 5.38; S 14.39.

Diacetoxymercury Derivative of (III). Compound (III) was obtained by heating a solution of 0.5 g of mercury oxide in 5 ml of glacial acetic acid and 0.2 g of (III) for 1 h. Upon dilution with 25-30 ml of water a white crystalline powder precipitated. It was filtered, washed with water and benzene, and dried at 100-105°. Yield was quantitative: mp 214-217° (dec.). Found, %: C 31.97; H 2.31. $C_{19}H_{16}Hg_2O_4$. Calc., %: C 32.21; H 2.20.

2-(1-Naphthyl)-4-thiophenecarboxylic Acid (II). To 2 g of (I) in 10 ml of pyridine was added in drops a solution of 1 g of potassium permanganate in a mixture of 12 ml of pyridine and 6 ml of water at a temperature of 50-60°. The manganese dioxide was filtered and the solvent was distilled. To the residue was added 10-15 ml of water and the mixture was acidified with hydrochloric acid with cooling. The precipitated crystals were filtered, washed with water, and dried in air. Yield 69%, mp 202-204° (from aqueous ethanol). Found, %: C 71.30; H 4.26. $C_{15}H_{10}O_2S$. Calc., %: C 70.84, H 3.96.

5-Methyl-2-[1-(3,4-dihydronaphthyl)]-thiophene (IV). The Grignard reagent was prepared from 10.5 g of 2-bromo-5-methylthiophene, 1.4 g of magnesium, and 30 ml of ether, to which a solution of 6.9 g of α-tetralone in 10 ml ether was added, maintaining boiling of the mixture. The mixture was heated for 30 min on the water bath and cooled; the magnesium complex was decomposed with ice. The ether layer was separated and the aqueous layer was extracted with ether. The ether extracts were dried with magnesium sulfate and the ether was distilled. To the obtained oil was added 3.5 ml of acetic anhydride and the mixture was heated for 30 min on a boiling water bath. Acetic anhydride was distilled and the residue was fractionated in vacuum. Yield of pale-yellow oil was 4.1 g, bp 204-208° (12 mm). Found, %: C 79.73; H 6.40. $C_{15}H_{14}S$. Calc., %: C 79.59; H 6.23.

Dehydration of Compound (IV). A mixture of 15 g of (IV) and 2.3 g of sulfur powder was heated at 220-240° until liberation of hydrogen sulfide ceased. The heavy oil was distilled in vacuum. Yield of (III) was 12.6 g (84%), bp 172-175° (4 mm). Found, %: C 79.95; H 5.38; S 14.32; $C_{15}H_{12}S$. Calc., %: C 80.31; H 5.38; S 14.29.

3,4-Diacetoxymercur-5-methyl-2-(1-naphthyl)-thiophene. This compound was obtained as described above. Yield was quantitative, mp 214-217° (dec.). Found, %: C 31.83; H 2.38. $C_{19}H_{16}Hg_2O_4$. Calc., %: C 32.21, H 2.20.

LITERATURE CITED

1. K. I. Vakhreeva, M. G. Viderker, P. I. Buchin, et al., "Synthesis of azomethine bases of the 2,2'-bithiophene series," Khim.-Farmats. Zh., No. 1, 24-25 (1972).
2. V. A. Smirnov, A. E. Lipkin, and T. B. Ryskina, "Synthesis and antimicrobial activity of 2-(2-aminothiazolyl-4)-thiophene and its derivatives," Khim.-Farmats. Zh., No. 6, 24-28 (1972).
3. K. I. Vakhreeva, A. E. Lipkin, T. B. Ryskina, et al., "Synthesis of azomethine bases of the 2,2'-bithiophene series having potential biological activity," Khim.-Farmats. Zh., No. 3, 24-27 (1973).
4. P. I. Buchin (editor), Problems of Immunology and Microbiology [in Russian], Kuibyshev (1971), p. 112.
5. N. V. Stulin and N. I. Putokhin, "Nitro derivatives of 2-(1-naphthyl)-thiophene," Khim. Geterotsikl. Soedin., No. 4, 512-515 (1965).
6. G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Meditsina, Moscow (1971), p. 539.