SYNTHESIS AND STUDY OF NITROGENOUS DERIVATIVES OF 2-THIENYLCINCHONINIC ACID

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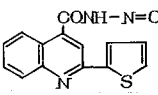
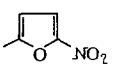
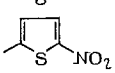
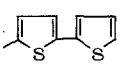
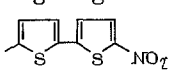
Derivatives of 4-quinolinecarboxylic acid, which is known as cinchoninic acid, possess definite biological activity. Thus, 2-phenylcinchoninic acid (atophane, or cinchophene) possesses antipyretic and analgesic action and is used in gout and neuralgia [1, 2]. 2-Thienylcinchoninic acid exerts a similar action [3]. There are reports on the synthesis of biologically active derivatives of 2-furyl- and 2-pyrrolylcinchoninic acids [4, 5] and also of antimalarial preparations based on 2-thienylcinchoninic acid [6].

TABLE 1. Arylidenehydrazides of 2-Thienylcinchoninic Acid



Compound	Ar	Yield (%)	Mp (in deg)	S, calcd. (%)	Empirical formula	Found (%)
IV	C_6H_5	90,4	246	8,98	$C_{21}H_{15}N_3OS$	9,19
V	o-$NO_2C_6H_4$	86,6	299	7,97	$C_{21}H_{14}N_4O_3S$	7,77
VI	m-$NO_2C_6H_4$	92,2	258	7,97	$C_{21}H_{14}N_4O_3S$	7,96
VII	p-$NO_2C_6H_4$	93,5	277	7,97	$C_{21}H_{14}N_4O_3S$	7,92
VIII		91,6	226	9,24	$C_{19}H_{13}N_3O_2S$	9,52
IX		93,7	289 (dec.)	8,18	$C_{19}H_{12}N_4O_4S$	7,98
X		91,3	249	17,67	$C_{19}H_{13}N_3OS_2$	17,13
XI		93,3	310 (dec.)	15,71	$C_{19}H_{12}N_4O_3S_2$	15,35
XII		86,6	259 (dec.)	21,59	$C_{23}H_{15}N_3OS_3$	21,92
XIII		56,7	303.5 (dec.)	19,60	$C_{23}H_{14}N_4O_3S_3$	19,71
XIV	p-$CH_3OC_6H_4$	96,6	261	8,28	$C_{22}H_{17}N_3O_2S$	8,04
XV	p-$(CH_3)_2NC_6H_4$	97,2	250	8,01	$C_{23}H_{20}N_4OS$	8,16
XVI	p-$(ClCH_2CH_2)_2NC_6H_4$	80,8	226	6,44	$C_{25}H_{22}Cl_2N_4OS$	6,60

Note. Compounds IV-VIII, X, XII, XIV-XVI were crystallized from a mixture of acetone and alcohol; the rest, from aqueous dimethylformamide.

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In the present work we describe the synthesis of 2-thienylcinchoninic hydrazide and products of its condensation with some aldehydes of the aromatic and heterocyclic series. The starting 2-thienylcinchoninic acid (I) and its ethyl ester (II) were prepared by the methods described in the literature, with certain changes [3]. 2-Thienylcinchoninic hydrazide (III) was obtained in quantitative yield by reaction of II with a large excess of hydrazine hydrate in ethyl alcohol. The corresponding arylidenehydrazides (IV-XVI, see Table 1) of 2-thienylcinchoninic acid were prepared by condensation of III with aldehydes of the aromatic or heterocyclic series in alcohol with heating.

The structures of the compounds synthesized were corroborated by elemental analyses and IR evidence. In the IR spectra there are absorption bands in the 1652-1664 cm^{-1} region, which are characteristic of the carbonyl group valence vibrations. In the case of nitro derivatives of the arylidenehydrazides of 2-thienylcinchoninic acid, well expressed absorption bands were observed in the 1520-1526 and 1341-1346 cm^{-1} regions; these are characteristic of the nitro group.

All the synthesized compounds were tested* for antimicrobial activity and proved inactive with respect to both Gram-positive forms of bacteria (Staphylococcus aureus and the potato bacillus) and also the Gram-negative forms (E. coli, typhus salmonella, Flexner and Sonne shigella, and Bacillus pyocyaneus).

EXPERIMENTAL

2-Thienylcinchoninic Acid (I). This compound was prepared by the method of [3]. The yield was 77%, mp 211° (from alcohol); lit. [3], mp 211° (from alcohol).

Ethyl 2-Thienylcinchoninate (II). Concentrated sulfuric acid (34 ml) was added dropwise to a suspension of 25.5 g of I in 255 ml of alcohol at 0-5°, the reaction mixture was boiled for 15 h, it was cooled, diluted with water, and neutralized with sodium carbonate. The precipitate which fell was filtered off, washed with water, and recrystallized from alcohol. The yield was 21.5 g (76%), mp 88°; lit. [3], mp 88°.

2-Thienylcinchoninic Hydrazide (III). Compound II (5.7 g) was dissolved in 25 ml of alcohol, 12.5 ml of hydrazine hydrate was added, and the reaction mixture was heated on a water bath. After 15-20 min a colorless, crystalline precipitate separated. After cooling, it was filtered off and washed with cold alcohol. The yield was quantitative, mp 237.5° (from alcohol); the substance is a colorless, crystalline material which is insoluble in water, difficultly soluble in ethanol or isopropyl alcohol, and readily soluble in acetone, glycerin, or dimethylformamide. Found, %: S 11.80. $C_{14}H_{11}N_3OS$. Calculated, %: S 11.93.

Arylidenehydrazides of 2-Thienylcinchoninic Acid (IV-XVI). A mixture of 0.005 mole of III with 0.005 mole of the appropriate aldehyde was dissolved in alcohol with warming and the solution was boiled for 3 to 4 h. After cooling, the solid which precipitated was filtered off, washed with alcohol, and recrystallized to constant mp.

The IR spectra of IV-XVI were measured in KBr disks (on an IKS-14 instrument), using a NaCl prism.

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*The microbiological tests were performed by T. B. Ryskina (Microbiology Department, Kuibyshev Medicinal Institute).