SYNTHESIS OF NITROGEN DERIVATIVES OF 2-SUBSTITUTED CINCHONINIC ACIDS

II. ARYLIDENEHYDRAZIDES OF 2-METHYL-, 2-(2'-THIENYLVINYL)-, AND 2-(5'-NITRO-2'-THIENYLVINYL)-CINCHONINIC ACIDS*

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Continuing our investigations [1-3] on the connection between chemical structure and biological activity in a series of 2-substituted cinchoninic acids, we have performed the synthesis and studied the antimicrobial properties of arylidenehydrazides of 2-methyl-, 2-(2'-thienylvinyl)-, and 2-(5'-nitro-2'-thienylvinyl)cinchoninic acids.

The initial 2-methylcinchoninic acid (I) and its ethyl ester (II) were obtained by methods described previously [4, 5] with some modifications. The reaction of (II) with a large excess of hydrazine hydrate in ethanol gave 2-methylcinchoninhydrazide (III) in almost quantitative yield.

The condensation of (III) with benzaldehyde and with 5-nitrofurfural in ethanol reproduced the synthesis of the benzylidenehydrazide (IV) and the 5-nitrofurfurylidenehydrazide (V) of 2-methylcinchoninic acid. A series of previously unreported arylidenehydrazides of 2-methylcinchoninic acids was obtained similarly by condensing (III) with a number of aromatic and heterocyclic aldehydes (VI-XVI, Table 1).

The reaction of (IV), (V), and (VIII-XIV) with 5-nitrothiophene-2-carbaldehyde gave the corresponding arylidenehydrazides of 2-(5'-nitro-2'-thienylvinyl) cinchoninic acid (XVII-XXV, Table 2).

The condensation of (IV) with thiophene-2-carbaldehyde in acetic anhydride was studied, and the benzylidenehydrazide of 2-(2'-thienylvinyl)cinchoninic acid (XXVI) was obtained in low yield. At the same time, (XXVI) and the other arylidenehydrazides of 2-(2'-thienylvinyl) cinchoninic acid were obtained in satisfactory yields by the condensation of 2-(2'-thienylvinyl)cinchoninhydrazide (XXVII) with aromatic and heterocyclic aldehydes in ethanol or isopropanol in a similar manner to the preparation of (IV-XVI) (XXVIII-XXXVII, Table 3).

The IR spectra of the arylidenehydrazides synthesized show absorption bands at 1667-1650 cm^{-1} that are characteristic for the stretching vibrations of amide carbonyl groups. The vibrations of the azomethine group are superposed on the absorption band of the aromatic rings. In compounds (VI-VIII, XI, XIII, XVII-XXV, XXVIII, XXX, XXXII, and XXXIV) well-defined absorption bands of NO_2 groups are observed in the 1526-1520 cm^{-1} and 1354-1342 cm^{-1} regions.

All the compounds synthesized were tested† for their antimicrobial activity in relation to Gram-positive and Gram-negative species of bacteria on simple nutrient agar at a standard concentration of the preparations of 400 $\mu g/ml$.

Weak antimicrobial activity in experiments with Bacillus mesentericus, Staphylococcus aureus, Escherichia coli, Pseudomonas pyocyanea and shigellas was shown by compounds (V, XI, XX, and XXII). The other substances proved to be inactive.

* For communication I, see [3].

†The microbiological tests were performed in the microbiology department of Kuibyshev Medical Institute.

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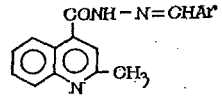
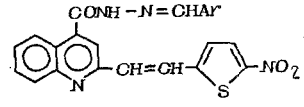
TABLE 1. Arylidenehydrazides of 2-Methylcinchoninic Acid



Compound	Ar	Yield (in %)	Melting point (in °C)	Found (%)			Empirical formula	Calculated (%)		
				C	H	N		C	H	N
VI	o-$NO_2C_6H_4$	93,6	234	64,47	4,15	16,57	$C_{18}H_{14}N_4O_3$	64,66	4,22	16,75
VII	m-$NO_2C_6H_4$	96,2	248	64,24	3,91	16,36	$C_{18}H_{14}N_4O_3$	64,66	4,22	16,75
VIII	p-$NO_2C_6H_4$	95,3	261	64,38	4,44	16,62	$C_{18}H_{14}N_4O_3$	64,66	4,22	16,75
IX	2'-furyl	95,2	191	68,94	4,60	15,12	$C_{16}H_{13}N_3O_2$	68,80	4,69	15,04
X	2'-thienyl	94,5	239,5	64,94	4,59	14,00	$C_{16}H_{13}N_3OS$	65,06	4,43	14,22
XI	5'-nitro-2'-thienyl	96,2	239(decomp)	56,80	3,58	12,08	$C_{16}H_{12}N_4O_3S$	56,50	3,82	12,36
XII	2', 2''-bithienyl-5'-yl	88,4	251	63,81	4,10	11,4	$C_{20}H_{15}N_3OS_2$	63,63	4,00	11,13
XIII	5'-nitro-2', 2''-bithienyl-5'-yl	54	262(decomp)	56,55	3,28	13,33	$C_{20}H_{14}N_4O_3S_2$	56,85	3,34	13,26
XIV	p-$CH_3OC_6H_4$	98,4	225,2	71,08	5,23	13,45	$C_{19}H_{17}N_3O_2$	71,44	5,36	13,15
XV	p-$(CH_3)_2NC_6H_4$	99,1	229	72,14	6,27	16,45	$C_{20}H_{20}N_4O$	72,26	6,06	16,85
XVI	p-$(ClCH_2CH_2)_2NC_6H_4$	81,3	197(decomp)	61,24	5,06	13,13	$C_{22}H_{22}Cl_2N_4O$	61,54	5,15	13,07

TABLE 2. Arylidenehydrazides of 2-(5'-Nitro-2'-thienylvinyl)cinchoninic Acid



Compound	Ar	Yield (in %)	Melting point (in °C)	Found (%)			Empirical formula	Calculated (%)		
				C	H	N		C	H	N
XVII	C_6H_5	60	273	64,18	3,63	13,21	$C_{23}H_{16}N_4O_2S$	64,47	3,76	13,07
XVIII	p-$NO_2C_6H_4$	70	287	58,54	3,78	14,98	$C_{23}H_{15}N_5O_5S$	58,34	3,95	14,79
XIX	2'-furyl	50	272 (decomp)	60,45	3,56	13,66	$C_{21}H_{14}N_4O_4S$	60,28	3,37	13,40
XX	5'-nitro-2'-furyl	65	273 "	54,45	2,55	15,46	$C_{21}H_{13}N_5O_6S$	54,42	2,83	15,10
XXI	2'-thienyl	40	277 "	57,82	3,66	12,58	$C_{21}H_{14}N_4O_3S_2$	58,05	3,25	12,89
XXII	5'-nitro-2'-thienyl	65	281 "	52,39	2,85	14,34	$C_{21}H_{13}N_5O_5S_2$	52,60	2,73	14,61
XXIII	2',2'-bithienyl-5'-yl	32	279	58,22	3,16	10,64	$C_{25}H_{16}N_4O_3S_3$	58,12	3,12	10,84
XXIV	5'-nitro-2'', 2'-bithienyl-5'-yl	14	293	53,68	2,75	12,23	$C_{25}H_{15}N_5O_5S_3$	53,46	2,69	12,47
XXV		40	279	62,79	3,66	12,49	$C_{24}H_{18}N_4O_4S$	62,87	3,95	12,21

TABLE 3. Arylidenehydrazides of 2-(2'-thienylvinyl)cinchoninic Acid

Compound	Ar	Yield (in %)	Melting point (in °C)	Found (%)			Empirical formula	Calculated (%)		
				C	H	N		C	H	N
XXVI	C_6H_5	89,9	269	71,72	4,48	11,06	$C_{23}H_{17}N_3OS$	72,04	4,46	10,95
XXVIII	p-$NO_2C_6H_4$	93,6	271	64,41	3,65	12,94	$C_{23}H_{16}N_4O_3S$	64,47	3,76	13,07
XXIX	2'-furyl	91,9	262	67,52	4,05	11,58	$C_{21}H_{15}N_3O_2S$	67,54	4,04	11,25
XXX	5'-nitro-2'-furyl	93,3	265(decomp)	60,37	3,36	13,13	$C_{21}H_{14}N_4O_4S$	60,28	3,37	13,38
XXXI	2'-thienyl	90,6	268—9	64,58	3,91	10,61	$C_{21}H_{15}N_3OS_2$	64,75	3,88	10,78
XXXII	5'-nitro-2'-thienyl	91,8	270(decomp)	57,92	3,23	12,46	$C_{21}H_{14}N_4O_3S_2$	58,05	3,24	12,89
XXXIII	2',2''-bithienyl-5'-yl	93,6	258—9	63,25	3,57	8,69	$C_{25}H_{17}N_3OS_3$	63,66	3,63	8,90
XXXIV	5''-nitro-2',2''-bithienyl-5'-yl	57,2	274	57,77	3,03	10,62	$C_{25}H_{16}N_4O_3S_3$	58,12	3,12	10,84
XXXV	p-$CH_3OC_6H_4$	97,8	242—3	70,04	4,66	10,22	$C_{24}H_{19}N_3O_2S$	69,71	4,63	10,16
XXXVI	p-$(CH_3)_2NC_6H_4$	98,4	244	70,01	5,15	12,94	$C_{25}H_{22}N_4OS$	70,39	5,19	13,13
XXXVII	p-$(ClCH_2CH_2)_2NC_6H_4$	65	205	62,05	4,57	10,53	$C_{27}H_{24}Cl_2N_4OS$	61,94	4,62	10,70

EXPERIMENTAL METHOD

The IR spectra were measured on a IKS-14 instrument in tablets with potassium bromide using a sodium chloride prism.

2-Methylcinchoninic Acid (I). A mixture of 29.4 g of isatin, 200 ml of acetone, and 170 ml of 20% caustic soda solution was boiled for 8 h and was then cooled to 0°C. The crystals of the sodium salt of (I) that deposited were separated off by decantation and were suspended in water and neutralized with acetic acid. The precipitate was filtered off and recrystallized from water. Yield 28 g (75%), mp 243°C; according to the literature [4], yield 50%, mp 243-245°C.

Ethyl 2-Methylcinchoninate (II). At 0-5°C, 37 ml of concentrated sulphuric acid was gradually added to a suspension of 18.7 g of (I) in 280 ml of ethanol, and then the reaction mixture was boiled for 15 h. The excess of ethanol was distilled off and the residue was diluted with water and neutralized with sodium carbonate. The precipitate that deposited was filtered off, washed with water, and recrystallized from ethanol. Yield 15 g (70%), mp 77°C.

2-Methylcinchoninhydrazide (III). To a solution of 21.5 g of (II) in 86 ml of ethanol was added 43 ml of hydrazine hydrate, and the reaction mixture was boiled for 1 h, and then it was cooled and was poured into an equal amount of water. The white crystalline precipitate of (III) was filtered off and washed with cold ethanol. Yield 19.7 g (98%), mp 178°C (from ethanol). Found %: C 66.01; H 5.49; N 20.72. $C_{11}H_{11}N_3O$. Calculated %: C 65.67; H 5.51; N 20.88.

Arylidenehydrazides of 2-Methylcinchoninic Acid (VI-XVI). A mixture of 2 g (0.01 mole) of (III) and 0.01 mole of the appropriate aldehyde was dissolved in ethanol with heating, and the solution was boiled for 1-2 h. After cooling, the precipitate that had deposited was filtered off, washed with ethanol, and recrystallized to constant melting point.

Arylidenehydrazides of 2-(5'-Nitro-2'-thienylvinyl)cinchoninic Acid (XVII-XXV). 5-nitrothiophene-2-carbaldehyde (3.5 g; 0.022 mole) was added to a solution of 0.02 mole of an arylidenehydrazide of 2-methylcinchoninic acid in acetic anhydride. The reaction mixture was kept at 160°C for 30 min and was then cooled and left overnight. Then the precipitate that had deposited was filtered off, washed with water and with ethanol, and crystallized to constant melting point.

2-(2'-Thienylvinyl)cinchoninic Acid (XXXVIII). This was obtained as described previously [6] with a yield of 60%, mp 292°C (from aqueous dioxane); according to the literature [6], mp 292-293°C (from allyl alcohol).

Ethyl 2-(2'-Thienylvinyl)cinchoninate (XXXIX). At 0-5°C, 94 ml of concentrated sulfuric acid was gradually added to a suspension of 28.1 g of (XXXVIII) in 700 ml of ethanol, and then the reaction mixture was boiled for 15 h, cooled, diluted with water, and neutralized with sodium carbonate. The product that deposited was extracted with ether, the ethereal solution was freed from resinous impurities with activated carbon, and, after filtration was evaporated on the water bath almost to dryness. Yield 19.4 g (63%), mp 71°C (from aqueous ethanol). Found %: C 69.71; H 4.82; N 4.69. $C_{18}H_{15}NO_2S$. Calculated %: C 69.87; H 4.86; N 5.53.

2-(2'-Thienylvinyl)cinchoninhydrazide (XXVII). A solution of 7.7 g of (XXXIX) in 115 ml of ethanol was treated with 25 ml of hydrazine hydrate, and the reaction mixture was boiled for 1 h. After the reaction mixture had cooled, the yellow crystalline precipitate was filtered off and was washed with cold ethanol. Yield almost quantitative, mp 211-212°C (from ethanol). Found %: C 64.97; H 4.67; N 14.17. $C_{16}H_{13}N_3OS$. Calculated %: C 65.06; H 4.43; N 14.22.

Arylidenehydrazides of 2-(2'-Thienylvinyl)cinchoninic Acids (XXVI, XXVIII-XXXVII). A solution of 1.5 g (0.005 mole) of (XXVII) and 0.005 mole of the appropriate aldehyde in ethanol, prepared with heating, was boiled for 2 h. [Compound (XXXIV) was obtained in butanol]. After cooling, the precipitate that had deposited was filtered off, washed with ethanol, and recrystallized from a mixture of ethanol and aqueous dimethylformamide to constant melting point.

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