AMINO ESTERS OF HETEROCYCLIC DICARBOXYLIC ACIDS

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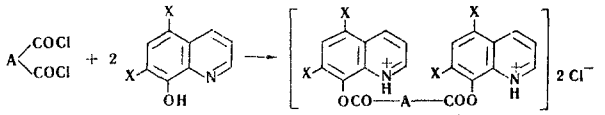
The corresponding amino esters and their complexes with 7,7,8,8-tetracyanoquinodimethane were obtained by the condensation of the acid dichlorides of furan-2,5-dicarboxylic acid and tetrahydrothiophene-2,5-dicarboxylic acid with 8-hydroxy- and 5,7-dibromo-8-hydroxyquinolines. Almost all of the compounds obtained have antimicrobial activity.

In a continuation of our previous investigations [1], we have accomplished the synthesis of amino esters of furan-2,5-dicarboxylic acid and tetrahydrothiophene-2,5-dicarboxylic acid and several complexes of them with tetracyanoquinodimethane. We have also studied the microbiological properties of the compounds described in the present communication and of those that we previously obtained in [1].

It is well-known that 8-hydroxyquinoline has antimicrobial activity [2], the mechanism of which consists in the formation of chelate complexes between it and the trace elements (particularly cobalt ions [3]) that are vitally necessary for the bacteria. It was therefore of interest to ascertain whether the activity is retained in amino esters – derivatives of 8-hydroxyquinoline as well as of 5,7-dibromo-8-hydroxyquinoline and heterocyclic dicarboxylic acids – and in the complexes obtained from them. The formation of complexes with metal ions is probable for hydrochlorides V-VII and analogous salts (XI and XII) with tetracyanoquinodimethane (TCQD) through the closely situated N–H and C=O groups and is apparently impossible for 1,1'-(3-oxapentamethylene)bis(3-hydroxy-1-ethylpiperidinium) dibromide (XIII) and the TCQD salt (XIV) of 2-[(2-bromoethoxy)ethyl]-1-methylpiperidine.

The amino esters were synthesized in good yields by the reaction of the acid dichlorides of furan-2,5-dicarboxylic acid and tetrahydrothiophene-2,5-dicarboxylic acid (I, II) with 8-hydroxy- and 5,7-dibromo-8-hydroxyquinolines (III, IV) (see Table 1).



I, II III, IV V–VIII

Tetrahydrothiophene derivatives give stable salts V and VI, while the salts are less stable in the case of furan derivatives. Thus, when salt VII is refluxed for 15-20 min in alcohol or acetone, it decomposes to form free base IX. In the reaction of IV with I, the reaction product is isolated immediately as free base X rather than salt VIII.

Complexes XI, XII, and XIV were obtained by an exchange reaction of the lithium salt of tetracyanoquinodimethane [4], respectively, with hydrochlorides V and VII and a quaternary salt – 1-[2-(2-bromoethoxy)ethyl]-1-methylpiperidinium bromide (XV).

A characteristic absorption band at 1730-1760 cm^{-1}, which corresponds to the C=O group of the amino ester, is observed in the IR spectra of V-VII and IX-XII, while the spectra of complexes XI, XII, and XIV contain an absorption band at 2180-2190 cm^{-1}, which corresponds to the C≡N group in salts with TCQD.

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TABLE 1. 2,5-Bis(8-quinolyloxycarbonyl)- and 2,5-Bis(5,7-dibromo-8-quinolyloxycarbonyl)furans and Tetrahydrothiophenes and Their Complexes with Tetracyanoquinodimethane

Comp.	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
V	225—227 [a]	$C_{24}H_{18}N_2O_4S \cdot 2HCl$	57,6	4,4	5,4	57,4	4,0	5,5	86
VI	196—198 [b]	$C_{24}H_{14}Br_4N_2O_4S \cdot 2HCl$	36,6	2,1	3,6	36,6	2,0	3,6	88
VII	191—193 [c]	$C_{24}H_{14}N_2O_5 \cdot 2HCl \cdot H_2O$	57,8	4,0	5,7	57,5	3,6	5,6	87
IX	218—220	$C_{24}H_{14}N_2O_5$	69,8	4,0	6,7	70,2	3,4	6,8	95
X	230—232 [d]	$C_{24}H_{10}Br_4N_2O_5$	39,3	2,0	3,5	39,7	1,4	3,8	88
XI	154—156 [e]	$C_{24}H_{20}N_2O_4S \cdot 2C_{12}H_4N_4 \cdot$	68,8	3,9	16,4	68,6	3,4	16,7	50
XII	169—171 [e]	$C_{24}H_{16}N_2O_5 \cdot H_2O \cdot 2C_{12}H_4N_4 \cdot$	69,3	4,1	17,0	68,7	3,1	16,7	72

[a]From isopropyl alcohol. [b]From ethyl acetate. [c]From ethanol. [d]From aqueous dimethylformamide. [e]From acetonitrile.

Preliminary data from microbiological investigations of V-VII and IX-XIV and of the previously synthesized 2,5-bis(1-methyl-3-piperidyloxycarbonyl)furan dihydrochloride [1], which were carried out on a series of test bacteria in the department of microbiology of the Saratov Medical Institute, demonstrated the presence of selective and specific antimicrobial action in all of the compounds except XIII. The products of the condensation of 8-hydroxyquinoline with thiophan-2,5-dicarboxylic acid (V and VI) have somewhat more active antimicrobial activity than the analogous derivatives of furan-2,5-dicarboxylic acid (VII and X). We have studied the antimicrobial activity of anion radical salts based on tetracyanoquinodimethane (XI, XII, and XIV). Detailed data from the microbiological investigations will be reported in a future communication.

EXPERIMENTAL

2,5-Bis(8-quinolyloxycarbonyl)tetrahydrothiophene Dihydrochloride (V). A solution of 2.6 g (12 mmole) of II in 25 ml of absolute benzene was added to 3.48 g (24 mmole) of III in 25 ml of absolute benzene at room temperature. The mixture was heated at 80° for 2 h, and the resulting precipitate was removed by filtration and washed with benzene to give 4.31 g (87%) of V as a light-yellow powder with mp 225-227°. Compounds VI, VII, IX, and X (see Table 1) were similarly obtained.

Salt of 7,7,8,8-Tetracyanoquinodimethane and 2,5-Bis(8-quinolyloxycarbonyl)tetrahydrothiophene (XI). A hot solution of 0.21 g (0.45 mmole) of V was added to a hot filtered solution of 0.1 g (0.5 mmole) of the lithium salt of tetracyanoquinodimethane in 30 ml of distilled water. The black crystals that formed were removed by filtration after 2 h and vacuum-dried over P_2O_5 to give 0.1 g (50%) of XI with mp 154-156° (with sublimation).

Compound XII (see Table 1) and the salt (XIV) of TCQD with 1-[2-(2-bromoethoxy)ethyl]-1-methylpiperidine [60%, mp 98-100° (from acetonitrile)] were similarly obtained. Found: N 15.6%. $C_{22}H_{25}BrN_5O$. Calculated: N 15.4%.

1-[2-(2-Bromoethoxy)ethyl]-1-methylpiperidinium Bromide (XV). An 8.1-g (35 mmole) sample of β,β'-dibromodiethyl ether [5] in 10 ml of hexane was added to 7 g (70 mmole) of 1-methylpiperidine in 10 ml of hexane, and the mixture was heated at 30° for 18 h. The resulting colorless crystals were removed by filtration to give 4.5 g (30%) of a product with mp 116-117° (from acetone). Found: C 36.0; H 6.5; N 4.7%. $C_{10}H_{21}Br_2NO$. Calculated: C 36.3; H 6.4; N 4.2%.

1,1'-(3-Oxapentamethylene)bis(3-hydroxy-1-ethylpiperidinium) Dibromide (XIII). This compound was similarly obtained after reaction for about a month. The yield of product with mp 190-192° (from acetone) was 30%. Found: C 43.7; H 7.7; N 5.7%. $C_{18}H_{38}Br_2N_2O_3$. Calculated: C 44.0; H 7.8; N 5.7%.

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