INVESTIGATION OF HETEROCYCLIC QUINONES

XXII. SYNTHESIS AND ANTIMICROBIAL ACTION OF SUBSTITUTED 2-PHENYLQUINAZOLINEQUINONES

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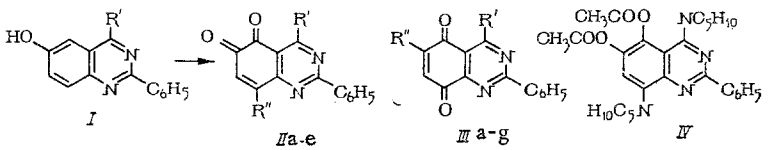
The synthesis and antimicrobial properties of a new class of heterocyclic quinones – quinazolinequinones – are described in the present paper. Compounds with high chemotherapeutic activity are known among aminonaphthoquinones [1-3]. It has been observed that the bacteriostatic action increases on passing from naphthoquinones to the corresponding quinoline analogs [3]. A number of amino derivatives of quinolinequinones display high antibacterial [4-6] and antitumorigenic activity [3,7,8]. Quinazolinequinones are 3-aza analogs of quinolinequinones. We therefore supposed that compounds that are of interest for chemotherapy might be detected among them. In addition, since there are substances with high antimicrobial activity among the N-substituted 2-phenyl-4-amino-6-hydroxyquinazolines that we have previously synthesized [9], it was of interest to study the antimicrobial properties of the quinones obtained from them.

The literature contains no data on the biological activity of quinazolinequinones except for a mention of the fact that unsubstituted quinazoline-5,8-quinone, which was first obtained in 1970, does not suppress the growth of staphylococci and streptococci in concentrations below 100 μg/ml but displays antitumorigenic action on sarcoma 180 at a concentration of 8.4 mg/kg [10].

The N-substituted 8-aminoquinazoline-5,6-quinones (II) described in this paper were synthesized by oxidative amination of 6-hydroxyquinazolines (I) (Table 1).



I *IIa-e* *III a-g* *IV*

R' = $NHCH_3$ (IIa); NHC_6H_5 (IIb); $N(CH_3)_2$ (IIc, d); NC_5H_{10} (IIe, IIIa, c); CH_3O (IIIb, d-g); R'' = NC_5H_{10} (IIa-c, e, IIId); $N(CH_2CH_2)_2O$ (IId, IIIe); CH_3O (IIIa, b); OH (IIIc) NHC_4H_9 (IIIf); $NHCH_3$ (IIIg).

Quinones II are dark-cherry-red crystalline substances that are stable on storage in the dark. Two characteristic carbonyl maxima are present at 1600-1700 cm^{-1} in their IR spectra. In addition, the spectra of quinones IIa (R' = $NHCH_3$) and IIb (R' = NHC_6H_5) contain absorption bands at 3300 cm^{-1}, which can be ascribed to NH stretching vibrations. We have previously synthesized the substituted quinazoline-5,8-quinones (III) [11], while IV was obtained by reductive acetylation of 2-phenyl-4,8-dipiperidinoquinazoline-5,6 quinone (IIe).

The action of the quinazolinequinones on the growth of a human type of tuberculosis bacillus (strain H 37 Rv), Gram-positive cocci (staphylococci, pneumococci, and streptococci) and bacilli (Bacillus anthracis and diphtheria inducer), Gram-negative bacilli (Escherichia coli, Bacillus pyocyaneus, Proteus, and typhus and dysentery inducers), and pathogenic fungi (candidosis inducers, microspores, and tricho-

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TABLE 1. N-Substituted 2-Phenyl-4,8-diaminoquinazoline-5,6-quinones

Comp.	Yield, %	IR spect. range, 3300 and 1600-1700 cm^{-1}	mp, °C	Found, %			Empirical formula	Calculated, %		
				C	H	N		C	H	N
IIa	55	3325 1652 1622	181—2	69,21	5,83	16,00	$C_{20}H_{20}N_4O_2$	68,95	5,79	16,08
IIb	89	3295 1645 1610	185—6	73,25	5,44	13,65	$C_{25}H_{22}N_4O_2$	73,65	5,44	13,65
IIc	85	— 1658 1612	190—1	69,57	6,08	15,59	$C_{21}H_{22}N_4O_2$	69,59	6,15	15,45
IId	42	— 1658 1642	196—8	65,55	5,50	15,60	$C_{20}H_{20}N_4O_3$	65,91	5,53	15,40

TABLE 2. Antibacterial Activity of Quinazoline-5,6- and -5,8-quinones (II and III)

Compound	Minimum bacteriostatic concn., μg/ml						
	staphylococcus 209-P	staphylococcus 295	pneumococcus 1	diphth. bacillus PW-8	bacillus anthracis 1312	tuberculosis bacillus without serum	tuberculosis bacillus with 10% serum
IIa	50	>100	>100	6,25	25,0	6,25	200
IIb	>100	>100	>100	>100	>100	>200	>200
IIc	>100	>100	>100	>100	>100	>200	>200
IId	>100	>100	>100	>100	>100	>200	>200
IIe	0,78—1,56	50	12,5	0,19	0,39	1,56	>200
IIIa	>100	>100	>100	>100	>100	>200	>200
IIIb	>100	>100	>100	>100	>100	>200	>200
IIIc	25—50	>100	50	25	12,5	6,25	>200
IIId	>100	50	12,5—25	12,5—25	12,5	>200	>200
IIIe	>100	>100	100	>100	50	>200	>200
IIIf	>100	>100	25	>100	>100	100	>100
IIIg	>100	>100	25	>100	>100	>200	>200

phytes) was studied by means of two successive cultures in a liquid medium. The Sutton medium was used in the experiments with the tuberculosis bacillus, while Hottinger broth was used for the other bacteria; the Saburo medium was employed for the fungi. The method adopted in the Laboratory of the Chemotherapy of Infectious Diseases and in the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute [12] was used.

It was found that none of the tested compounds depress the growth of Gram-negative bacteria in concentrations of 200 μg/ml and below or the growth of pathogenic fungi in concentrations of 1 mg/ml and below.

Several preparations displayed bacteriostatic action against Gram-positive bacteria and the tuberculosis bacillus. The results of these experiments are presented in Table 2, from which it is seen that two of the five compounds of the quinazoline-5,6-quinone group (IIa and IIe) retard the growth of Gram-positive bacteria, of which staphylococcus and the diphtheria and the anthrax bacilli are more sensitive than streptococcus and pneumococcus. The activity of IIe can be rated as high, while that of IIa is no more than moderate. Both of these preparations have considerable tuberculostatic action, and the minimum bacteriostatic concentration (MBC) is 1.56-6.25 μg/ml, but only in media without serum. One's attention is directed to the fact that the introduction of a piperidine residue into the 4 position sharply increases the activity as compared with the corresponding methylamino and (to an even greater degree) phenylamino derivatives. At the same time, of the 4-substituted 2-phenyl-6-hydroxyquinazolines, the most active are those with a phenylamino group in the 4 position [9]. This enables us to conclude that the mechanism of the bacteriostatic action of the quinazoline-5,6-quinones differs from that of the corresponding 6-hydroxyquinazolines.

It has been observed that some highly active quinolinequinones can be converted to the diacetates of hydroquinones that are just as active [3]. This is apparently an exceptional characteristic, since the reductive acetylation of highly active quinone IIe gives diacetate IV, which does not display antimicrobial properties in any of the tested objects.

Of the seven compounds of the quinazoline-5,8-quinone group (III), five (IIIc-IIIg) displayed weak activity against several Gram-positive bacteria. In this case, pneumococcus proved to be the most sensitive microorganism, and this distinguishes the spectrum of action of the quinazoline-5,8-quinones from that of quinazoline-5,6-quinones. One of the preparations (IIIc) displayed moderate tuberculostatic activity in testing in a medium without serum (MBC 6.25 μg/ml). This effect was absent in experiments in which a serum medium was used. From the correlations between the structure and action, one must note the positive effect of a piperidine residue in the 4 or 6 position.

The most active compound (IIe) did not display chemotherapeutic action in tests on mice infected with Gram-positive bacteria. The antibacterial properties of the investigated quinazolinequinones are primarily of theoretical interest. They attest to the fact that the search for new antimicrobial preparations in the quinazoline-5,6- and 5,8-quinone series holds promise.

EXPERIMENTAL

Oxidation of N-Substituted 2-Phenyl-4-amino-6-hydroxyquinazolines (Ia-c). A 10-mmole sample of the quinazoline was introduced into a solution of 0.02 g of copper acetate and 60 mmole of secondary amine in 15 ml of methanol, and the mixture was stirred under oxygen until gas absorption ceased (from 3 to 6 h, depending on the basicity of the secondary amine). In the case of quinone IId, 120 mmole of morpholine was used. The resulting precipitate was removed by filtration, washed with alcohol and ether, and recrystallized from benzene (for quinones IIa,b), ethyl acetate (IIc), or dioxane (IId). The yields and physical constants of the quinones are presented in Table 1.

2-Phenyl-4,8-dipiperidino-5,6-diacetoxyquinazoline (IV). A mixture of 0.4 g of IIe, 25 ml of acetic anhydride, 2 ml of pyridine, and 2 g of zinc dust was refluxed for 10 min, during which the solution became colorless. The mixture was cooled, the zinc dust was removed by filtration, and the filtrate was vacuum evaporated to dryness. The residue was extracted with hot acetone, and the extract was vacuum evaporated to give 0.3 g (63%) of IV with mp 227-228° [from ethyl acetate–heptane (1:1)]. Found %: C 69.01; H 6.60; N 11.37. $C_{28}H_{32}N_4O_4$+. Calculated %: C 68.83; H 6.60; N 11.09.

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