SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF PRODUCTS OF CONDENSATION OF ALLOXAN WITH 2-METHYLQUINOLINE DERIVATIVES

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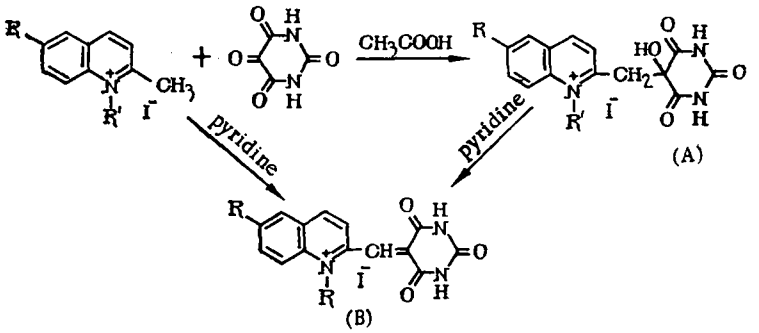
We reported in [1, 2] that the products of the condensation of alloxan, 1-methyl-, and 1,3-dimethylalloxan with 2-methylquinoline derivatives display pronounced antibacterial and antifungal action. Some of these compounds are effective as growth stimulators for grain and legume crops [3].

Quarternary salts of quinaldine in glacial acetic acid solution are known to react with alloxan and its 1,3 derivatives to give stable aldol-condensation products of the type (A) [1, 2, 4]. The stability of these compounds is explained by their structure. The hydroxyl group is stabilized by the presence of the neighboring electron-accepting carbonyl groups, and the IR absorption spectra indicate that intermolecular hydrogen bonds are also formed. The reaction products were obtained by heating the starting compounds for a short time.

We studied the behavior of the hydroxy compounds (A) in pyridine solution. It was found that even at room temperature water is lost and the colored compounds (B) are formed. Direct condensation of 2-methylquinoline salts with alloxan in pyridine solution gave the unsaturated compounds B and not the hydroxy compounds A.



The double bond in the condensation product is conjugated and gives rise to absorption bands in the visible region at 475-535 nm. Substitutents that donate electrons (CH_3, OCH_3, C_2H_5) cause a small (5-11 nm) hypsochromic shift of the absorption maximum, and substituents that withdraw electrons (Cl, Br, NO_2) cause a corresponding bathochromic effect (Tables 1 and 2). Conjugation of the quinoline and pyrimidine rings is confirmed by the IR spectra, in which there are a number of intense bands in the regions 1735-1705, 1720-1650, 1670-1610, and 1600-1500 cm^{-1}. The frequencies 1735-1705 and 1720-1650 cm^{-1} correspond to the stretching frequencies of the carbonyl groups of the barbituric acid residue. The decrease in the absorption frequencies of the carbonyl groups compared with the corresponding hydroxy products is apparently explained by the increase in the electron density on the barbituric ring when it is conjugated with the quinoline nucleus [5].

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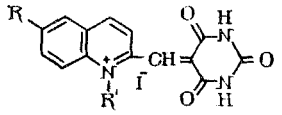
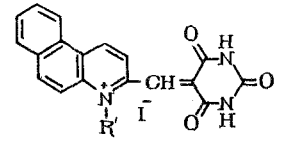
TABLE 1. Products of the Condensation of Alloxan with 2-Methylquinoline Derivatives (B)



Compound	R	R'	Yield, %	Melting point	λ_{max}, nm	log ε	Found, %		Empirical formula	Calculated, %	
							N	I (Cl)		N	I (Cl)
I	H	CH_3	53	236	493	3,79	10,19; 10,21	30,93; 30,85	$C_{15}H_{12}IN_3O_3$	10,27	31,03
II	CH_3	CH_3	60	224	488	3,75	9,65; 9,58	29,50; 29,47	$C_{16}H_{14}IN_3O_3$	9,79	29,56
III	CH_3O	CH_3	50	114	484	3,65	9,47; 9,50	28,53; 28,69	$C_{16}H_{14}IN_3O_4$	9,54	28,66
IV	C_2H_5O	CH_3	55	211	488	3,75	9,07; 8,99	27,87; 27,75	$C_{17}H_{16}IN_3O_4$	9,27	27,99
V	Cl	CH_3	62	213	503	3,73	8,80; 8,73	— —	$C_{15}H_{11}ClIN_3O_3$	8,87	—
VI	Br	CH_3	60	230	505	3,73	8,02; 7,95	— —	$C_{15}H_{11}BrIN_3O_3$	8,11	—
VII	$NHCOCH_3$	CH_3	48	116	480	3,68	11,40; 11,48	26,65; 26,79	$C_{17}H_{15}IN_4O_4$	11,66	26,87
VIII	NO_2	CH_3	55	350	507	3,81	11,96; 12,07	27,83; 27,98	$C_{15}H_{11}IN_4O_5$	12,33	27,97
IX	H	C_2H_5	48	242	490	3,93	9,69; 9,73	29,32; 29,30	$C_{16}H_{14}IN_3O_3$	9,79	29,56
X	CH_3O	C_2H_5	49	242	489	3,78	9,20; 9,19	28,01; 27,90	$C_{17}H_{16}IN_3O_4$	9,27	27,99
XI*	H	C_6H_5	45	113	526	3,70	9,45; 9,30	7,80; 7,75	$C_{20}H_{14}ClN_2O_3$	9,51	7,98
XII	H	$\alpha=C_{10}H_7$	41	284	544	3,85	7,98; 7,89	24,20; 24,27	$C_{24}H_{16}IN_3O_3$	8,06	24,34
XIII	CH_3	$\alpha=C_{10}H_7$	40	321	532	3,83	7,65; 7,73	23,59; 23,48	$C_{25}H_{18}IN_3O_3$	7,85	23,70
XIV	CH_3O	$\alpha=C_{10}H_7$	40	307	534	3,80	7,48; 7,53	22,80; 22,76	$C_{25}H_{18}IN_3O_4$	7,62	23,01

*Isolated as the perchlorate.

TABLE 2. Products of the Condensation of Alloxan with 2-Methylbenzo[f]quinoline Derivatives (B)



Compound	R'	Yield, %	Melting point, deg	λ_{max}, nm	log ε	Found, %		Empirical formula	Calculated, %	
						N	I		N	I
XV	C_6H_5	50	294	518	4,00	7,80; 7,87	24,31; 24,28	$C_{24}H_{16}IN_3O_3$	8,06	24,34
XVI	$4=CH_3C_6H_4$	47	299	519	3,86	7,73; 7,79	23,65; 23,59	$C_{25}H_{18}IN_3O_3$	7,85	23,70
XVII	$4=CH_3OC_6H_4$	51	317	520	3,88	7,50; 7,47	22,93; 22,90	$C_{25}H_{18}IN_3O_4$	7,62	23,01
XVIII	$2=CH_3OC_6H_4$	47	291	532	3,80	7,53; 7,58	22,87; 22,97	$C_{25}H_{18}IN_3O_4$	7,62	23,01

EXPERIMENTAL

Pharmacology

Medicinal uses of derivatives of 2-methylquinoline and barbituric acid have been suggested [6, 7], and we therefore studied the *in vitro* antimicrobial action of the synthesized compounds on some forms of pathogenic bacteria and on fungi of the genus *Candida*. As can be seen from Table 3, the compounds were active towards *Staphylococcus aureus* (minimum bacteriostatic concentration varied from 7.8 to 31.25 μg/ml). Gram-negative bacteria of the intestinal group (*Escherichia coli*, *Salmonella typhi*), anthrax, and rhinoscleroma bacilla were sensitive to the compounds in doses from 31.25 to 125 μg/ml. Concentrations of from 7.8 to 125 μg/ml destroy fungi of the genus *Candida*. For a given class of compound the antimicrobial action of the compounds differed in strength by a factor of 2-16, depending on the nature of the substituents on the quinoline nucleus. Some of the most active compounds were those with a methyl group on the hetero nitrogen atom of the quinoline nucleus.

The antibacterial and antifungal properties of these compounds were found to be similar to those of the analogous hydroxy compounds A. Elimination of water lowered their antistaphilococcus action somewhat, while their antifungal action remained unchanged [1, 2].

Chemistry

The quarternary salts of 1-methyl and 1-ethylquinaldine were all obtained by the same general method [8, 9]. 6-Aminoquinaldine was obtained by the reduction of 6-nitroquinaldine, and the base 6-acetylaminoquinaldine by acylation of 6-aminoquinaldine [10]. The quarternary salt of 1-methyl-6-aminoquinaldine iodide was synthesized by hydrolysis of the 6-acetylaminoquinaldine salt.

1-Phenyl-2-[(2,4,6-trioxohexahydropyrimidinylidene-5)methine]benzo[f]quinoline Iodide (XII). A mixture of 1-phenylbenzo[f]quinaldine iodide (0.80 g; 2 mmole) and alloxan monohydrate (0.38 g; 2 mmole) dissolved in absolute pyridine (2 ml) is carefully ground. This suspension is then heated on a water bath for 30 min, allowed to cool, and the dye precipitated with ether. The precipitate is dissolved in absolute acetone (150 ml) and chromatographed on a column filled with a special type of aluminum oxide. The band containing the dye is eluted with ethyl alcohol, and after removal of the solvent, the pure compound is obtained.

1-Phenyl-2[(2,4,6-trioxohexahydropyrimidinylidene-5)methine]quinoline Perchlorate (XI). A mixture of 1-phenylquinaldine perchlorate (0.64 g; 2 mmole) and alloxan monohydrate (0.32 g; 2 mmole) is dissolved in dry pyridine (2 ml) and left at room temperature for 24 h. The dye is then precipitated with ether and purified by chromatography as described above.

TABLE 3. Antimicrobial Activity of the Products of the Condensation of Alloxan with 2-Methylquinoline Derivatives

Compound	Minimum bacteriostatic concentration, μg/ml					
	Staph. aureus	E. coli	Candida albicans	B. antracoides	Kl. rhinoscleromatis	S. typhi
I	7,80	31,25	31,25	62,5	31,25	31,25
II	31,25	31,25	7,80	31,25	62,5	31,25
III	15,62	31,25	31,25	62,5	62,5	62,5
IV	15,62	31,25	31,25	62,5	62,5	31,25
VI	15,62	31,25	31,25	62,5	62,5	62,5
VII	31,25	31,25	31,25	31,25	62,5	31,25
IX	31,25	31,25	31,25	62,5	62,5	62,5
XI	62,5	125,0	125,0	125,0	62,5	62,5
XII	31,25	62,5	125,0	125,0	62,5	62,5
XIII	15,62	62,5	62,5	62,5	31,25	62,5
XIV	31,25	62,5	62,5	62,5	31,25	62,5
XV	62,5	62,5	62,5	62,5	62,5	62,5
XVI	15,62	31,25	31,25	62,5	31,25	62,5
XVII	15,62	62,5	62,5	62,5	31,25	62,5
XVIII	15,62	62,5	125,0	125,0	62,5	62,5

Other condensation products were obtained by a similar method.

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SYNTHESIS AND PHARMACOLOGY OF MONOMERIC COUMARINS AND THEIR COPOLYMERS

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In view of the diversity of biological activity possessed by the many naturally occurring monomeric coumarin derivatives [1-5], it seems promising to search among them for physiologically active compounds potentially useful as drugs. The poor water solubility of this group of compounds, however, greatly restricts their pharmacological investigation and clinical use. Consequently, the synthesis and investigation of water-soluble coumarin derivatives would be very valuable for practical medicine. As is known, such compounds can be prepared by introducing N-alkyl radicals into the coumarin molecules [5, 6] or by copolymerizing them through the double bond in the 3,4 position of the lactone ring with vinylic comonomers [7-9]. The latter method is the more promising since it greatly prolongs the action of the compounds and in some cases increases it, which is of practical importance.

Proceeding from what has been said in [9, 10], we have synthesized copolymers of coumarin (XX) and a number of its synthetic and natural derivatives substituted in the benzene ring at positions 5, 6,7, 7, and 7,8.

The properties of the monomeric coumarins are indicated in Table 1 and those of their copolymers with N-vinylpyrrolidone (VP) are indicated in Table 2.

It was found that, as with coumarin, polymerization with all of the coumarin derivatives proceeds by a radical mechanism through the double bond in the 3,4 position of the α-pyrone ring. The structure of the resulting polymeric coumarin derivatives was verified on the basis of chemical data and their UV, IR, and NMR spectra [10].

The synthesis of copolymers of VP with coumarins substituted in the α-pyrone ring is of theoretical and practical interest in being a practical method of synthesizing copolymers of

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