3-PHENACYL-2-QUINOXALONES AND 3-PHENACYLIDENE-3,4-DIHYDRO-2-QUINOXALONES

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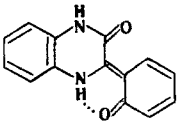
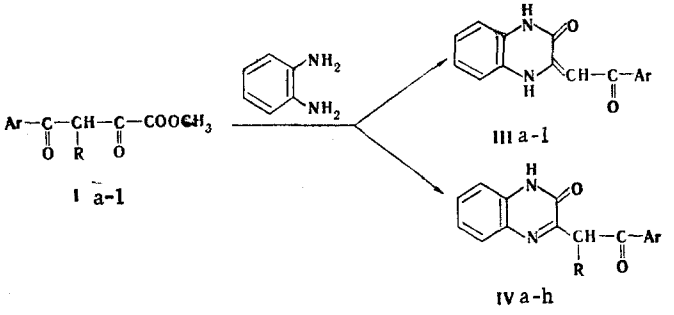
A number of 2-quinoxalone derivatives were synthesized by reaction of aroylpyruvic acid esters with o-phenylenediamine. It was established by IR and UV spectroscopy that compounds with a substituent attached to the α-carbon atom of the phenacyl group exist in the 3-phenacyl-2-quinoxalone form, whereas unsubstituted 2-quinoxalones have a 3-phenacylidene-3,4-dihydro-2-quinoxalone structure. A relationship between the spectral shifts of the long-wave maximum and the σ^+ para substituent constants on passing from the molecular forms to the ionic forms of 3-phenacylidene-3,4-dihydro-2-quinoxalones was established.

The reaction of acylpyruvic acids and their esters (I) with o-phenylenediamine (II) leads to the corresponding 2-quinoxalone derivatives [1]. It was established by PMR spectroscopy that the products of the reaction of aroylpyruvic acids with II have 3-phenacylidene-2-quinoxalone (III) structures. This structure, which has an exocyclic ethylene bond, is stabilized by an intramolecular hydrogen bond between the hydrogen atom of the NH group in the quinoxalone ring and the oxygen atom of the carbonyl group of the phenacylidene substituent [2]. This structure is the most favorable not only for quinoxalones with phenacyl substituents in the 3 position but also for 3-phenyl-2-quinoxalones, which, as previously shown, exist in the 3-(cyclohexa-3,5-dien-2-onylidene)quinoxal-2-one form [3]:



Continuing our search for physiologically active compounds among quinoxaline derivatives we have synthesized a number of 2-quinoxalones by reaction of esters I with o-phenylenediamine:



See Table 1 for the Ar and R values for IIIa-l and IVa-h.

During a study of the UV spectra of the synthesized compounds we observed that quinoxalones with α-substituents in the phenacyl grouping have λ_{max} at 330-350 nm; this is close to the position of λ_{max} for quinoxalones that do not have a phenacyl substituent in the 3 position [2]. Thus interaction between the quinoxalone ring and the benzoyl chromophore is

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TABLE 1. Characteristics of 2-Quinoxalone Derivatives III and IV

Compound	R	Ar	mp, °C*	Found, %			Empirical formula	Calc., %			UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}			Yield, %
				C	H	N		C	H	N		$\nu_{C=O}$	amide $\nu C=O$	ν_{NH}	
IIIa	H	C_6H_5	266—267	72,3	4,2	10,5	$C_{16}H_{12}N_2O_2$	72,7	4,5	10,7	441 (4,46)	1617	1691	3058	99
IIIb	H	p-$C_6H_4CH_3$	229—230	72,8	4,9	9,7	$C_{17}H_{14}N_2O_2$	73,1	5,0	10,0	438 (4,40)	1610	1680	3049	96
IIIc	H	p-$C_6H_4OCH_3$	245—246	68,4	4,5	9,2	$C_{17}H_{14}N_2O_3$	68,8	4,7	9,5	440 (4,40)	1613	1685	3055	92
IIId	H	p-C_6H_4Cl	270—271	64,1	3,4	9,3	$C_{16}H_{11}ClN_2O_2$	64,3	3,7	9,4	440 (4,50)	1612	1689	3050	95
IIIe	H	p-C_6H_4F	256—257	68,5	3,7	9,7	$C_{16}H_{11}FN_2O_2$	68,8	3,9	9,8	440 (4,52)	1610	1683	3049	91
IIIf	H	p-$C_6H_4C_2H_5$	242—243	73,8	5,5	9,3	$C_{18}H_{16}N_2O_2$	74,0	5,5	9,6	440 (4,40)	1614	1681	3060	89
IIIg	H	p-C_6H_4Ph	302—303	77,4	4,4	8,5	$C_{22}H_{16}N_2O_2$	77,6	4,7	8,4	448 (4,55)	1610	1690	3100	90
IIIh	H	p-$C_6H_4NO_2$	304—305	62,0	3,3	13,2	$C_{16}H_{11}N_3O_4$	62,1	3,6	13,4	439 (4,31)	1600	1680	3100	45
IIIi	H	2,5-$(CH_3)_2C_6H_3$	231—232	73,8	5,5	9,5	$C_{18}H_{16}N_2O_2$	74,0	5,5	9,6	430 (4,30)	1618	1713	3060	97
IIIj	H	2,4,6-$(CH_3)_3C_6H_2$	257—258	74,2	5,6	9,2	$C_{19}H_{18}N_2O_2$	74,5	5,9	9,2	430 (4,32)	1614	1680	3050	87
IIIk	H	α-$C_{10}H_7$	268—269	76,2	4,2	9,3	$C_{20}H_{14}N_2O_2$	76,4	4,5	9,0	445 (4,48)	1610	1690	3090	98
IIIl	H	p-C_6H_4Br	284—285	55,6	2,9	7,9	$C_{16}H_{11}BrN_2O_2$	55,8	3,2	8,1	443 (4,53)	1600	1680	3040	99
IVa	CH_3	C_6H_5	113—114	73,2	4,8	9,7	$C_{17}H_{14}N_2O_2$	73,3	5,0	10,0	336 (3,79)	1690	1670	3080	42
IVb	C_2H_5	C_6H_5	181—182	74,1	5,8	9,3	$C_{18}H_{16}N_2O_2$	73,9	5,5	9,6	340 (3,99)	1660	1670	3100	60
IVc	$CH(Ph)_2$	C_6H_5	290—291	81,0	5,1	9,1	$C_{29}H_{22}N_2O_2$	80,9	5,1	9,0	354 (3,96)	1690	1670	3030	45
IVd	$CH(Ph)_2$	p-C_6H_4Br	262—263	68,7	4,3	4,6	$C_{29}H_{21}BrN_2O_2$	68,4	4,1	4,5	347 (4,28)	1690	1665	3030	53
IVe	$CH(Ph)_2$	p-$C_6H_4CH_3$	280—282	81,3	5,5	6,2	$C_{30}H_{24}N_2O_2$	81,0	5,4	6,3	357 (4,09)	1730	1665	3030	65
IVf	Br	C_6H_5	215—216	56,1	3,5	8,0	$C_{16}H_{11}BrN_2O_2$	56,0	3,2	8,2	353 (3,98)	1700	1680	3060	94
IVg	Br	p-C_6H_4Br	226—227	45,2	2,1	6,4	$C_{16}H_{10}Br_2N_2O_2$	45,5	2,4	6,6	358 (3,95)	1690	1670	3100	92
IVh	Br	2,4,6-$(CH_3)_3C_6H_2$	197—198	69,2	3,5	5,9	$C_{19}H_{17}BrN_2O_2$	68,9	3,3	6,1	353 (3,98)	1700	1680	3060	97

*See the experimental section for the recrystallization solvents.

TABLE 2. Shift of the Long-Wave Maximum in the UV Spectra of 3-Phenacylidene-3,4-dihydro-2-quinoxalones on Passing from the Molecular Forms to Their Ionic Forms

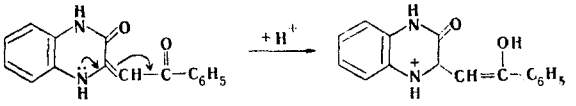
Compound	Molecular form, $\nu \cdot 10^{-3}$ (log ε)	Ionic form, $\nu \cdot 10^{-3}$ (log ε)	$\Delta\nu \cdot 10^{-3}$
IIIc	22,70 (4,40)	20,00 (4,81)	2.70
IIIb	22,80 (4,40)	20,64 (4,78)	2,16
III g	22,32 (4,55)	20,18 (4,83)	2,14
III f	22,67 (4,46)	20,73 (4,66)	1,95
IIIi	22,57 (4,53)	20,71 (4,83)	1,86
IIIh	22,78 (4,31)	21,58 (4,87)	1,20

absent in these quinoxalones, and this is in agreement with a structure with an endocyclic double bond (IV).

A shift of the long-wave maxima to 440-450 nm is observed in the UV spectra of quinoxalones that do not have α-substituents in the side chain; this indicates interaction between the quinoxalone and benzoyl chromophores through an exocyclic ethylene bond.

The differences in the structures of the quinoxalones that are determined by the presence of an α-substituent in the phenacyl grouping are due to steric factors. Structure III specifies coplanarity of the pyrazine and H-chelate rings. Because of the steric hindrance that arises in the case of interaction of the quinoxaline carbonyl group and the α-substituent in the phenacyl grouping the structure with an exocyclic ethylene bond is impossible for IV. The formation of a hydrogen bond that stabilizes this structure is impossible in the case of a trans orientation of the benzoyl group and the NH group of the quinoxaline ring. Steric hindrance is absent in the structure with an endocyclic double bond because of deviation of the substituents attached to the methylidyne group in the side chain from the plane of the ring, and this structure is therefore the most favorable one for IV.

The transition from alcohol solutions of the synthesized quinoxalones III to solutions in trifluoracetic acid is accompanied by a bathochromic shift of λ_{max} (see Table 2), which (in analogy with α-quinolylpyruyic acid esters) is explained by better transmission of the effect of the substituents through the conjugated system when enamine III is protonated to give cation V via the scheme [2]



III V

The bathochromic shifts of the long-wave maxima on passing from the molecular forms to the ionic forms correlate satisfactorily with the σ^+ para substituent constants. The calculated correlation dependence is linear and can be represented by the equation $\Delta\nu = 1.95 \cdot 10^{-3} + 0.993\sigma^+$, where correlation coefficient r is 0.993, and the mean square deviation S is 0.0059.

The dependence found in this research showed that electron-donor substituents stabilize the ionic form of quinoxalones III, whereas electron-acceptor substituents have a destabilizing effect.

Quinoxalones IV also are converted to a protonated form in trifluoroacetic acid, and this constitutes evidence that an intramolecular hydrogen bond does not participate in stabilization of the ionic form.

During a study of the IR spectra of the compounds obtained in this research we observed that there are substantial differences in the positions of the absorption bands of the corresponding stretching vibrations of the carbonyl groups in the spectra of the two types of 2-quinoxalones. The absorption band at 1660 cm^{-1} in the spectra of quinoxalones that do not have a carbonyl group in the side chain is due to the absorption of the quinoxalone carbonyl group [2]. This band is present at 1660-1670 cm^{-1} in the IR spectra of quinoxalones with an endocyclic double bond. The absorption of the ketone carbonyl group in the spectra of IV is

observed at 1690-1700 cm^{-1}. In the spectra of III, which are vinylogs of α-keto amides, there is an increase in the absorption corresponding to the stretching vibrations of the amide carbonyl group to 1680-1690 cm^{-1} and a decrease in the absorption corresponding to the stretching vibrations of the ketone carbonyl group to 1600-1620 cm^{-1} because of the formation of an intramolecular hydrogen bond in analogy with unsaturated amino ketones.

All of the synthesized compounds have weak absorption at 3030-3110 cm^{-1} due to the stretching vibrations of the NH bonds in the quinoxaline rings.

EXPERIMENTAL

The UV spectra of solutions of III and IV in alcohol, trifluoroacetic acid, and concentrated sulfuric acid were recorded with an SF-4 spectrophotometer at sample concentrations ranging from 10^{-3} to 10^{-5} M. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer (with NaCl and LiCl prisms).

Quinoxalone Derivatives IIIa-l. A solution of an equimolar amount of o-phenylenediamine in alcohol was added to a solution of methyl aroylpyruvate in alcohol, and the mixture was allowed to stand for 30 min. The resulting precipitate was removed by filtration and recrystallized from dimethylformamide.

Quinoxalone Derivatives IVc-e. Equivalent amounts of methyl β-diphenylmethylaroylpyruvate and o-phenylenediamine were refluxed in alcohol for 10 min, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from alcohol.

Quinoxalone Derivatives IVf-h. A solution of an equimolar amount of o-phenylenediamine in benzene was added to a solution of methyl β-bromoaroylpyruvate in benzene, and the resulting precipitate was removed by filtration and recrystallized from glacial acetic acid.

The yields, melting points, and the results of analysis of the synthesized compounds are presented in Table 1.

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