ALKYLATION AND REDUCTION REACTIONS IN THE ISOQUINO[2,3-*a*]QUINAZOLINE SERIES

V. M. Kisel', V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev

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Protonation and methylation of 5-oxo-7,12-dihydro-5H-isoquino[2,3-a]quinazoline occur at the $N_{(6)}$ atom, while methylation of 5-oxo- and 6-methyl-5-oxo-6,6a,7,12-tetrahydro-5H-isoquino[2,3-a]quinazolines takes place at the $N_{(13)}$ atom; the degree of stereoselectivity varies depending on the presence of a substituent attached to $N_{(13)}$. Based on PMR spectral analysis utilizing the nuclear Overhauser effect, we have established the structure and studied the conformational behavior of the tosylate derivatives of cis-13-methyl-, trans-13-methyl-, and cis-6,13-dimethyl-5-oxo-6,6a,7-12-tetrahydro-5H-isoquino[2,3-a]quinazolinium ions.

We have previously [1] reported the synthesis of 5-oxo-7,12-dihydro-5H-isoquino[2,3*a*]quinazoline (I) and its protonated salts, hydrobromide Ia and perchlorate Ib. In the present paper we describe our study of the chemical and spectral properties of these compounds and their derivatives, which were prepared as part of our research effort into biologically active compounds among the series of little-studied isoquino[2,3-*a*]quinazoline heterocyclic derivatives.

Formally the structure of isoquinoquinazoline I represents a 1,2-dialkylated quinazolone; it was expected [2], therefore, that protonation and alkylation should take place at the carbonyl oxygen atom of the $N_{(6)}$ atom in the ring. Based on the IR spectral data for the protonated salts Ia, b, which exhibit carbonyl group stretching vibrational bands at 1710 cm^{-1} and $C{=}N^+$ group stretching bands at 1635 cm^{-1} [1], protonation of the precursor compound I occurs at the $N_{(6)}$ atom. Alkylation with methyl tosylate also takes place at this position; the alkylation reaction is carried out by heating the mixture of starting materials in nitromethane. The IR spectra of the alkylation product, which can be isolated in the form of tosylate IIa or perchlorate Ib, retain both the C=O (1710) and $C{=}N^+$ (1625 cm^{n1}) group stretching vibration bands. The structure of perchlorate Ib was also verified by its PMR spectrum: saturation at the resonance frequency for the newly introduced methyl group {6-CH_3} under nuclear Overhauser effect experimental conditions led to a 6% increase (η = 0.06) in the intensity of the 7-H proton singlet, while the 4-H proton signal did not manifest a large NOE value.

The free isoquinazoline base I and its quaternary salt IIa are easily reduced with sodium borohydride in alcohol solution to give 5-oxo- and 6-methyl-5-oxo-6,6*a*,7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazolines (III and IV, respectively). The carbonyl group is not reduced under these conditions, as indicated by the presence in the IR spectra of the reduction products of the corresponding stretching vibrational bands in their IR spectra, and the presence of methine proton signals in their PMR spectra, attest to the fact that reduction takes place at the $C_{(6a)}{=}N_{(6)}$ double bond. The structures of these tetrahydroisoquinoquinazolines III and IV contain asymmetric carbon atoms, thus the methylene group protons are diastereotopic and magnetically nonequivalent. The PMR spectra of these compounds (in $CDCl_3$ or C_6D_6) exhibit AB- and ABX-type spin system multiplets. The form of the signal for the methylene group protons in the 7-position in compound III was found to be insensitive to the effect of solvent in which the spectrum was recorded: the 7-H and 6*a*-H protons in the spectrum of this compound, recorded in DMSO-D_6, give rise to an A_2X spin system, in which the vicinal coupling constant (SSCC) is equal to 7.3 Hz (see scheme at top of page 318).

In contrast to dihydroisoquinoquinazoline I, the tetrahydro derivatives undergo alkylation at the $N_{(13)}$ bridgehead atom, resulting in the formation of two possible isomeric salts, the products of cis- and trans- addition of a methyl group relative to the 6*a*-methine hydrogen atom. An interesting feature of this reaction is that the stereochemistry differs, depending on the nature of the 6-R group in the starting material III and IV. Thus, methylation of compound III with methyl tosylate in nitromethane leads to the formation, in 85% yield, of a mixture of approximately equal amounts of the trans- and cis-13-methyl-5-oxo-6,6*a*,7,12-tetrahydro-5H-isoquino[2,3*a*]quinazolinium tosylates (V and

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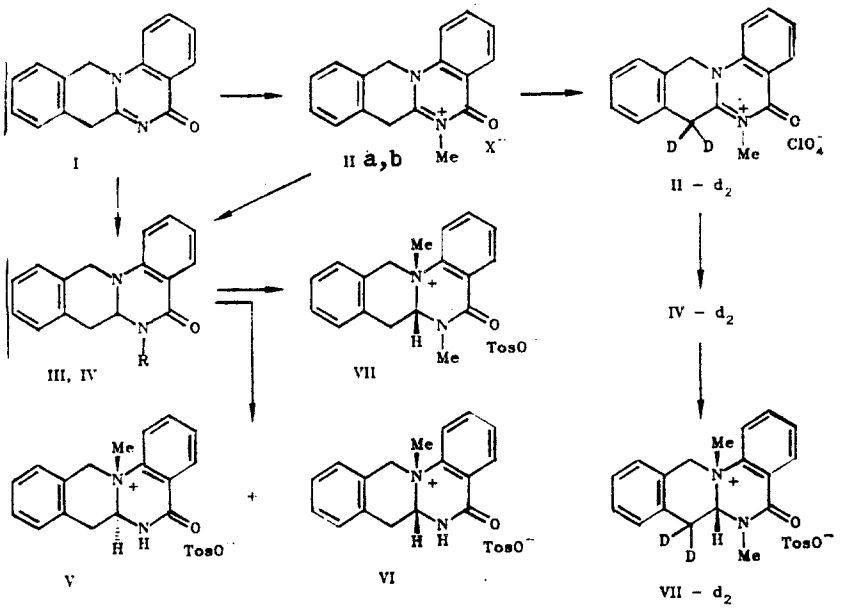
TABLE 1. Spectral Characteristics of Compounds II-VII

Compound	IR spectrum, ν, cm^{-1}		Solvent	PMR spectrum										
				shifts, δ, ppm							SSCC, Hz			
	C=O	N-H		6α-H_X, d	7-H_A, d.d	7-H_B, d.d	12-H_A, d	12-H_B, d	6-R, s	13-CH_3, s	J_{AX}	J_{BX}	J_{AB}^7	J_{AB}^{12}
IIa,b	1710	—	CF_3COOD	—	4,80 s		5,81 s		4,05	—	—	—	—	—
III	1670	3180	$CDCl_3$	5,04 d.d	3,34	3,11	4,78	4,21	8,04	1,1	9,5	4,8	15,8	16,1
			DMSO-D_6	4,96 t	3,01 d		4,89	4,23	8,44	1,1	7,3		—	16,9
			C_6D_6	4,40 d.d	2,95	2,52	4,19	3,64	7,84	1,1	9,7	3,9	16,1	16,1
IV	1645	—	$CDCl_3$	4,90 d.d	3,18	2,92	4,85	4,46	3,21	—	9,8	4,5	16,0	16,5
			DMSO-D_6	5,16 d.d	3,25	2,94	5,00	4,46	3,08	1,1	9,3	4,8	15,0	16,8
			C_6D_6	4,04 d.d	2,70	2,15	4,35	3,87	2,79	—	11,2	4,0	15,7	17,6
V	1685	3100	CF_3COOD	5,85 d.d	3,90	3,55	5,76	5,23	—	3,52	5,4	11,2	18,6	14,7
VI	1685	3060	CF_3COOD	5,87 d.d (0,6)*	3,95 (0,18)	3,34 (0,18)	5,43 (0,24)	5,06 (0,24)	—	3,89 (0,3)	5,9	5,6	19,3	15,9
VII	1670	—	CF_3COOD	5,84 d.d	3,87	3,01	5,78	5,45	3,58	3,93	5,5	10,6	18,7	16,1

*The values of the relaxation times T_1 are given in parentheses.



II a X=TosO⁻, b X=ClO₄; III R=H, IV R=CH₃

VI, respectively), each of which was isolated in pure form. Quaternization of the 6-methyl-substituted isoquinoquinazoline IV, on the other hand, proceeds in a more stereoselective manner; cis-6,13-dimethyl-5-oxo-6,6*a*,7,12-tetrahydro-5H-isoquino[2,3*a*]quinazolinium tosylate (VII) was formed and isolated exclusively in 70% yield. The sites of methyl group introduction and the isomeric structural assignments for the quaternary salt products V-VII were determined based on their PMR spectral data and on the results of NOE experiments. For example, a {13-CH_3} experiment in the spectrum of compound V results in an intensity increase in the signal of only one proton, namely the 12-H_A proton.* This result indicates not only that methyl group addition has occurred at the $N_{(13)}$ atom, but also that salt V has the trans-structure. In the opposite case we would have predicted an equally large effect for the 6*a*-H_X proton as well as in the cis-isomer, since examination of molecular models suggests that this proton is the same or a shorter distance away from the 13-CH_3 group as either of the 12-H protons. This conclusion was supported by the results of a {12-H_B} experiment, which revealed a substantial NOE value for the 6*a*-H_X proton (η = 0.07). The three-dimensional picture which emerges from these experiments, that one of the methylene group protons at $C_{(12)}$ is proximate to the 13-CH_3 group, while the other methylene proton is proximate to the methine 6*a*-H_X proton, is consistent with one isomeric structure, namely the trans-isomer V. The second product isolated from the methylation reaction of isoquinoquinazoline III was assigned the alternative structure for the cis-isomer VI; this structural assignment was confirmed by the results of a {13-CH_3} NOE experiment, which gave a value of $\eta_{6a\text{-H}}$ = 12%. A somewhat unexpected result of this experiment, however, was the absence of a significant NOE effect for the 12-H protons, apparently due to different rates of relaxation for the methine 6*a*-H proton and these methylene protons. It is clear from the values of the T_1 relaxation times for the aliphatic protons in compound VI (Table 1) that the 12-H protons relax 2.5 times faster than the 6*a*-H proton; this would be expected to be accompanied by a corresponding decrease in its NOE. The results also suggest considerable conformational flexibility for the structure of compound VI, since only in this event would the T_1 values for the pairs of 12-H and 7-H protons be expected to coincide so precisely.

An analogous {13-CH_3} NOE experiment to those described above was carried out for the spectrum of the quaternary salt VII; intensity increases were observed for the signals of both the 12-H protons as well as the methine 6*a*-H_X proton (the total magnitude of the NOE for the entire group of closely spaced signals was 20%). The observed effect for the 6*a*-H_X proton does not provide unequivocal evidence for the cis-structure of this compound; however, since it may arise as well from the three-dimensional proximity of the 6*a*-H_X proton to one of the methylene protons 7-H_A; the multiplet for the 7-H_A proton coincides with the singlet signal for the irradiated 13-CH_3 group. The validity of the isomeric structural assignment is affirmed, nevertheless, by the large NOE value (η = 0.14) observed for the

*Here and below, the aliphatic protons in the ring are designated using the generally accepted [3] classification scheme for AB- and ABX-spin systems; the more downfield proton of two interacting (coupled) geminal protons is assigned the index A.

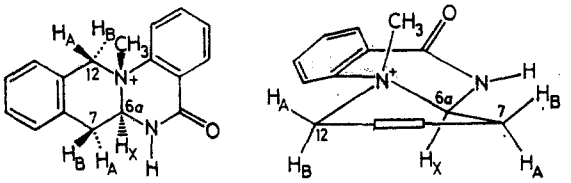


Fig. 1. Preferred conformation for the tetrahydroisoquinolinium ring in quaternary salt V.

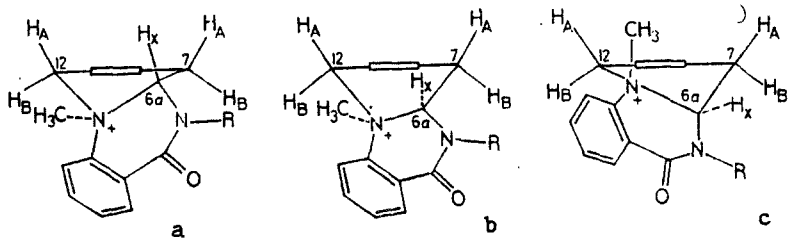


Fig. 2. Possible conformations for the tetrahydroisoquinolinium ring in cis-quaternary salts VI and VII.

geminal 7-H_B proton. In order to circumvent the deleterious influence of the 7-H protons on the results of the {13-CH_3} experiment, we exchanged them for deuterium in the quaternary salt IIa. This compound was stored in deuterotrifluoroacetic acid solution for 2 days, then treated with sodium perchlorate in heavy water, to give 6-methyl-5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolinium-7,7-D_2 perchlorate (II-D_2); the isotopic purity of this material was found to be 70% based on PMR spectral analysis, and was not altered during the course of subsequent chemical reactions. Reduction of this compound (II-D_2) with sodium borohydride in deuteromethanol was followed by alkylation under the same conditions as for the protonated analog IV. Exchange of the 7-H protons by deuterium did not have any effect on the results of the NOE experiment, and the concomitant simplification of the signal multiplicity for the 6*a*-H_X proton made it possible to evaluate the contribution of each proton to the total NOE value. A repeat {13-CH_3} experiment yielded the following NOE value: $\eta_{6a\text{-}H_X} = 0.11$; $\eta_{12\text{-}H_A} = \eta_{12\text{-}H_B} = 0.05$, which verify the cis-structural assignment for salt VII.

The PMR spectra of the quaternary salts V-VII, coupled with the results of the NOE experiments, provide valuable information concerning the conformational behavior of the tetrahydroisoquinoquinazolinium ring in these compounds. Based on the values of the vicinal SSCC J_{AX} and J_{BX} in the ABS spin systems for the 6*a*-H and 7-H protons we have determined the dihedral angles formed by the planes passing through the $C_{(6a)}C_{(7)}H_A$ and $C_{(6a)}C_{(7)}H_B$ atoms and the plane passing through the $C_{(7)}C_{(6a)}H_X$ atoms (φ_{AX} and φ_{BX}, respectively). These calculations were made using a modified Karplus equation taking into account the electronegativity of the substituents and their orientation relative to the coupled protons [4]. For the quaternary salt V having the trans-structure the observed and calculated values of J_{AX} and J_{BX} coincided at dihedral angle values of $\varphi_{AX} = 45°$ and $\varphi_{BX} = 175°$. Analysis of a molecular model for this compound reveals that the calculated dihedral angle values correspond to a "distorted half-chair conformation, in which all of the carbon atoms in the tetrahydroisoquinolinium ring are located virtually in one plane, while the quaternary nitrogen atom is withdrawn from the plane (Fig. 1). The tetrahydroisoquinolinium ring in quaternary salt VII exists predominantly in the same conformation (Fig. 2a): the calculated dihedral angle values for this compound are 45° (φ_{AX}) and 165° (φ_{BX}). In this conformation the distance between the 13-CH_3 methyl group and each of the 12-H methylene protons is identical, which is in excellent agreement with the results of the {13-CH_3} NOE experiment described above.

In the PMR spectrum of quaternary salt VI the values of the vicinal SSCC are small and approximately equal, which makes it impossible to assign unambiguously the signals for the 7-H protons as cisoid or transoid relative to the 6*a*-H_X methine proton. For this reason, solution of the modified Karplus equation for the series of coupling constants yields four possible sets of dihedral angle values for φ_{AX} and φ_{BX} (43, 130°; 1218, 41°; 39, 41°; 41, 39°); none of these dihedral angle sets has any physical reality, however, probably due to the conformational mobility or flexibility of the tetrahydroisoquinolinium ring in this compound, as noted earlier. Analysis of molecular models for this compound permits us to identify three relatively stable conformations (Fig. 2); two of these conformations are classified as distorted half-chairs, differing in which of the atoms $N_{(13)}$ or $C_{(6a)}$ is projected out of the tetrahydroisoquinolinium ring (*a* and c, respectively, while the third conformation is a tub conformation (b).

In order to estimate the degree to which one or another of these conformations is favored, we have calculated the expected vicinal SSCC values for each of these possible conformations, and then, assuming that the observed spectral SSCC values represented an average for all three states, we were able to determine mole fractions for conformers *a*, b, and c, which were found to be 0.27, 0.35, and 0.38, respectively.

In conclusion, a substituent attached to $N_{(6)}$ exerts an influence not only on the stereoselectivity of alkylation of isoquinoquinazolines III and IV, but also on the conformational flexibility or mobility of the resulting quaternary salts having a cis-structure, such as VI and VII. The lower conformational flexibility of compound VII relative to VI is probably due to steric hindrance arising from the methyl group at $N_{(6)}$, which devaluates conformations b and c; only in conformation *a* is this methyl group adequately removed in space from the $C_{(7)}$ methylene group. We cannot exclude that the methyl group attached to $N_{(6)}$ exerts an analogous effect on the stereoselectivity of alkylation of isoquinoquinazoline IV, since in the trans-diastereomer the methyl group is located close to the $C_{(7)}$ methylene group, which should make this diasteromer sterically less favored. We have not obtained any evidence, however, to suggest that compound IV exists preferentially in this or another diastereomer form.

EXPERIMENTAL

Melting points were determined on a Boetius heating stage. IR spectra using KBr pellets were recorded on a Pye Unicam SP3-300 spectrophotometer. PMR spectra of solutions were obtained on a Bruker WP-100 spectrometer (at 100.13 MHz) versus TMS as internal standard; SSCC values were determined with an accuracy of 0.1 Hz.

The results of C, H, N, Cl, and S elemental analysis agreed with calculations.

6-Methyl-5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolinium Tosylate (IIa, $C_{17}H_{15}N_2O^+ \cdot C_7H_7SO_3^-$). A solution of 2.5 g (10 mmoles) isoquinoquinazoline I and 2.42 g (13 mmoles) methyl tosylate in 25 ml nitromethane was refluxed for 2 h and treated with ether. The resulting oily precipitate was triturated in dry ether, then dissolved with a little heating in a minimum amount of 2-propanol. The resulting precipitate which was deposited as the solution cooled was separated by filtration, mp 175°C (from nitromethane). Yield 1.35 g (31%).

6-Methyl-5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolinium Perchlorate (IIb, $C_{17}H_{15}N_2O^+ \cdot ClO_4^-$). Obtained upon treatment of an aqueous alcohol solution of tosylate IIa with an aqueous solution of sodium perchlorate, mp 274°C (decomp.) (from acetic acid).

5-Oxo-6,6*a*-7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazoline (III, $C_{16}H_{14}N_2O$). To a solution of 2.5 g (10 mmoles) of compound I in 50 ml ethanol was added 0.62 g (15 mmoles) sodium borohydride in small portions. When the vigorous reaction had ceased, the mixture was refluxed for 15 min, and the solvent was then evaporated; the residue was treated with 20 ml of 10% aqueous NaOH solution, and the solid precipitate was removed by filtration and washed with water and alcohol; mp 201°C (from 2-propanol). Yield 2.22 g (89%).

6-Methyl-5-oxo-6,6*a*-7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazoline (IV, $C_{17}H_{16}N_2O$). This was prepared from compound IIa in an analogous manner to compound III; mp 167°C (from 2-propanol). Yield 63%.

trans- and cis-13-Methyl-5-oxo-6,6*a*-7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazolinium Tosylates (V, $C_{17}H_{17}N_2O^+ \cdot C_7H_7SO_3^-$ and VI, $C_{17}H_{17}N_2O^+ \cdot C_7H_7SO_3^-$). A solution of 1.25 g (5 mmoles) isoquiniquinazoline III and 1.86 g (10 mmoles) methyl tosylate in 25 ml nitromethane was refluxed for 20 h. The resulting precipitate consisted of the pure trans-isomer V, mp 229°C. Yield 0.65 g (30%).

To obtain the cis-isomer VI, the reaction mixture (without preliminary removal of the trans-isomer V), was treated with 80 ml acetone, and the resulting precipitate was removed by filtration (it consisted of a mixture of the trans- and cis-isomers in a 2:1 ratio, based on PMR spectral analysis); the filtrate was allowed to stand an additional 5-7 days. This resulted in deposition of crystals of the pure cis-isomer VI, which were collected by filtration and washed with nitromethane; mp 207°C (from nitromethane). Yield 0.55 g (25%).

cis-6,13-Dimethyl-5-oxo-6,6*a*,7,12-tetrahydro-5H-isoquino[2,3*a*]quinazolinium Tosylate (VII, $C_{18}H_{19}N_2O^+ \cdot C_7H_7SO_3^-$). Prepared in an analogous manner to compound V; mp 226°C (from nitromethane). Yield 70%.

6-Methyl-5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolinium-7,7-D_2 Perchlorate (II-D_2). With mild heating compound IIa (1.73 g, 4 mmoles) was dissolved in 6 ml deuterotrifluoroacetic acid, and allowed to stand for 2 days; excess sodium perchlorate solution in heavy water was added, and the resulting precipitate was filtered, washed with heavy water, and dried. Yield 1.17 g (82%) of a light yellow crystalline substance.

6-Methyl-5-oxo-6,6*a*=7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazoline-7,7-D_2 (IV-D_2). This was obtained in an analogous manner to its protonated analog IV, using a fourfold excess of sodium borohydride and deuteromethanol as solvent.

6,13-Dimethyl-5-oxo-6,6*a*-7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazolinium-7,7-D_2 Tosylate (VII-D_2). Prepared in an analogous manner to its protic counterpart compound VII.

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PHYSICOCHEMICAL PROPERTIES AND STRUCTURE OF ANTHRAPYRIMIDINE AND ITS DERIVATIVES

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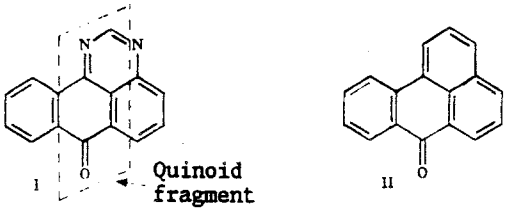
The method of electron spectroscopy entailing quantum-chemical calculations and the IR absorption spectra demonstrated the existence of the mono-, di-, and triprotonated forms of anthrapyrimidine and its derivatives in acidic solutions. The order of the protonation of the anthrapyrimidine molecule was established. It was shown that the two nitrogen atoms add protons; the third proton binds with the oxygen atom of the carbonyl group. In the molecule, the positive charge is localized within the pyrimidine ring. The energy characteristics of the anthrapyrimidine and its protonated forms were calculated.

Derivatives of anthrapyrimidine are utilized as dyes and pigments for polymer materials [1, 2] and, in this connection, the study of their physicochemical properties acquires large significance. The basicity and spectroscopic characteristics of some derivatives of anthrapyrimidine were presented in [3-5]. The present paper is dedicated to the study of the structure and protonation of anthrapyrimidine and its 6-chloro derivative by spectroscopic and quantum-chemical methods.

The anthrapyrimidine (I) should possess, on the one hand, the properties of benzoquinones since it has the quinoid fragment in the molecule and, on the other hand, the properties of the benzanthrone (II).



I II

The molecule of compound (I) is a π-electron analog of the benzanthrone (II), 3-azabenzanthrone (III), and 1-azabenzanthrone (IV) (cf. Table 1). These substances actually have similarity according to a series of characteristics: the carbonyl bands in the IR absorption spectra and the maximum of the long-wave band λ_{max} in the electronic spectrum of compound (I) occur between the values of the λ_{max} for 6-chloroanthrapyrimdine (V) and compound (III).

It is known that the integral intensities of the absorption bands of the functional groups in the IR spectra characterize the electron-optical properties of molecules.

The values of $\nu_{C=O}$ for compounds (I)-(III) and (V) are almost the same (cf. Table 1). Consequently, the electron-optical characteristics of the C=O groups of these compounds are close.

It was previously established [4] that compound (II) is protonated at the oxygen atom of the carbonyl group with the localization of the positive charge on the carbon atom within the molecule (see scheme on page 322).

For anthrapyrimidine and its derivatives, the ring nitrogen atoms possess higher basicity than the carbonyl oxygen atom; it was therefore to be expected that the protonation proceeds primarily at the nitrogen atoms. In fact, the pK_b values of pyrimidine (—1.3 [6]), hydroxyphenol (—3.3 [6]), and benzanthrone (—5.01 [4]) confirm this conclusion.

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