INVESTIGATION OF THE STRUCTURE OF 1,2-DIHYDRO-3-(2-HYDROXYPHENYL)-4-NITROPYRAZOL-5(3H)-ONE BY SPECTROSCOPIC AND QUANTUM-CHEMICAL METHODS

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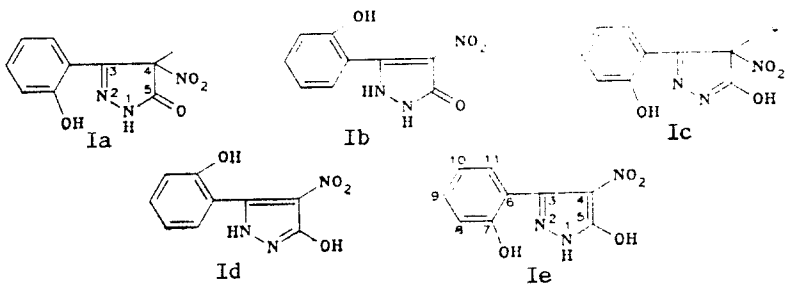
The structure of the previously synthesized 1,2-dihydro-3-(2-hydroxyphenyl)-4-nitropyrazol-5(3H)-one (I) was studied by ^1H and ^{13}C NMR, IR, and electronic spectra. It was established that the NMR spectra of compound (I) do not contain signals for the H atom at position 4 and the C atoms of the carbonyl groups; in the crystalline state and in solutions the IR spectra do not contain $\nu_{C=O}$ bands, while the electronic spectra do not contain absorption in the region of 250 nm. On the basis of the foregoing it is concluded that compound (I) exists in the OH form. The distribution of π-electron density in the molecule of (I) and the nature of the bands in its electronic absorption spectrum were studied by quantum–chemical methods in the PPP approximation.

Derivatives of pyrazole-5-one exhibit a wide range of biological activity, including pharmacological activity, and the synthesis and investigation of new compounds of this series therefore remain urgent. In the present work we give the results from a spectroscopic (NMR, IR, and EA) and quantum-chemical (in the PPP approximation) investigation of the structure of 1,2-dihydro-3-(2-hydroxyphenyl)-4-nitropyrazol-5(3H)-one (I), the synthesis of which from 3-nitro-4-aminocoumarins or 3-nitro-4-chlorocoumarin was first described in [1, 2] and was described more recently in [3].

As known, derivatives of pyrazolone are characterized by the capacity for tautomeric transformations (the CH, NH, and OH forms), the equilibrium between which changes depending on the nature of the solvent, the nature and position of the substituents in the ring, the temperature, and the concentration [4-6]. According to the data presented in the above-mentioned papers, the structure of (I) can be represented by the structures (Ia-e).



Theoretical and experimental examination of the tautomeric equilibrium for the isolated molecule indicate increased stability for the CH form of pyrazolone [6, 7]. However, it can be expected that the nitro group at position 4 of the pyrazolone ring, which has strong electron-withdrawing characteristics and is capable of forming an intramolecular hydrogen bond with the adjacent OH group, will shift the equilibrium toward the OH form. In fact, it was found in [8] that the analog of (I), i.e., 1-phenylethyl-3-methyl-4-nitropyrazol-5-one, exists only in the OH form both in the crystalline state and in solutions. In addition, the OH group at the o position of the phenyl substituent at position 3 is favorably situated for the formation of a hydrogen bond with the N atom at position 2, and this may additionally stabilize the tautomeric form (Ie) of compound (I).

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TABLE 1. π-Bond Energy (E_π), the σ-Energy (E_σ), the Heats of Atomization (ΔH), the Solvation Coefficients (M_{solv}), and the π-Dipole Moments ($\vec{\mu}$) of the Tautomeric Forms of (I)

Compound	E_π, eV	E_σ, eV	ΔH, eV	M_{solv}	$\vec{\mu}$ D
Ib	26,18	53,28	110,06	8,37	13,82
Id	25,95	53,26	110,05	6,39	6,74
Ie	26,73	53,24	110,80	6,79	7,60

The heats of atomization (ΔH) of the tautomers (Ib, d, e), which we calculated for the gas phase by the PPP method do in fact make it possible to give preference to form (Ie) (Table 1).

The gain in energy for structure (Ie) is achieved through π conjugation (π-bond energy). The difference in the ΔH values of the investigated structures amounts to about 0.7 eV. In the solutions, however, the energies of the tautomers (Ib) and (Id, e) will become closer as a result of solvation. This is favored by the values of the solvation coefficients M_{solv} of the tautomeric forms and their π-dipole moments calculated in terms of the solvation model (Table 1). The solvation coefficient of the less-stable tautomer (Ib), which characterizes the capacity of the molecule for electrostatic interaction with the solvent, is 1.23-1.31 times larger than the coefficients of tautomers (Id) and (Ie). Consequently, the decrease in the energy for the tautomer (Ic) as a result of solvation will also be greater than for (Id) and (Ie).

$$E_{solv} = M_{solv}\ (1 - 1/\varepsilon).$$

Comparison of the π-dipole moments of the investigated molecules in the ground state leads to a similar conclusion. Electrostatic (dipole–dipole) interaction with the solvent for form (Ib), for which $\vec{\mu}$ is 1.82-2.05 times larger, must be stronger than for forms (Id) and (Ie), i.e., the total energy of the indicated tautomers will become closer together as a result of solvation.

The structures (Ia) and (Ic) were not calculated but (as mentioned above), the existence of form (Ia) in solution is possible for this type of compound.

Thus, it is not possible to eliminate completely the possibility of an equilibrium between the given tautomeric forms in the solutions on the basis of the foregoing.

In order to obtain experimental evidence for the existence of (I) in one or the other form or of an equilibrium between them we studied its NMR, IR, and electronic absorption spectra in the crystalline state and in solutions.

NMR Spectra. In the PMR spectra in CD_3OD solution there are signals at 6.91 and 7.30 ppm corresponding to the four protons of the phenyl ring, but the signal for the proton of the heterocycle at position 4 is absent (3.6-3.9 ppm [9]). This rules out the presence of the CH form of (I) in CD_3OD solution.

Earlier it was shown for the case of substituted pyrazolin-5-ones that the tautomeric forms of pyrazolones can be distinguished by the use of ^{13}C NMR spectroscopy without the use of the results from other methods [10]. Analysis of the ^{13}C NMR spectrum of (I) makes it possible to choose between the OH and NH tautomeric forms. Thus, the ^{13}C NMR spectrum does not contain signals in the region characteristic of the carbonyl atoms (160-210 ppm [11]), which would be observed in the case where the tautomeric forms (Ia) and (Ib) were realized. The signals in the region of 116.63-157.08 ppm can be explained in terms of a tautomeric equilibrium between the OH forms of the compounds (Id) and (Ie): $C_{(5)}$ 157.05, $C_{(4)}$ 119.34, $C_{(3)}$ 142.31, $C_{(6)}$ 116.97, $C_{(7)}$ 157.08, $C_{(8)}$ 116.63, $C_{(9)}$ 131.34, $C_{(10)}$ 120.22, and $C_{(11)}$ 132.42 ppm.

IR Absorption Spectra. In the IR absorption spectrum of (I) in the crystalline state and in solutions in chloroform, dioxane, and acetonitrile there are no strong absorption bands in the region of 1630-1720 cm^{-1}, in which the $\nu_{C=O}$ band of the CH and NH forms of the pyrazolones appear [4, 5]. A band of medium intensity with a diffuse maximum in the region of 1645 cm^{-1} belongs to the δ_{H_2O} deformation vibrations, since it is known that compound (I) crystallizes in the form of the monohydrate [3]. Consequently, both in the crystalline state and in solutions with nonpolar and polar solvents compound (I) is not present in the tautomeric CH and NH forms in appreciable amounts (within the sensitivity limits of the method).

In the spectrum of (I) in the crystalline state in the region of the ν_{OH}, ν_{NH}, and ν_{H_2O} stretching vibrations there is a broad diffuse band at 3550-2000 cm^{-1}, against the background of which there are bands with maxima at 3530, 3390, 3180, and 2600 cm^{-1}. In the spectrum in chloroform solution at a concentration of about 10^{-3} M the first two of them are observed in the form of narrow bands at 3620-3600 and 3460-3450 cm^{-1}, while the broad band as a whole becomes somewhat narrower (3600-2800 cm^{-1}). Here the center of gravity of the broad band is displaced little compared with that in the IR spectrum of (I) in potassium bromide (Fig. 1).

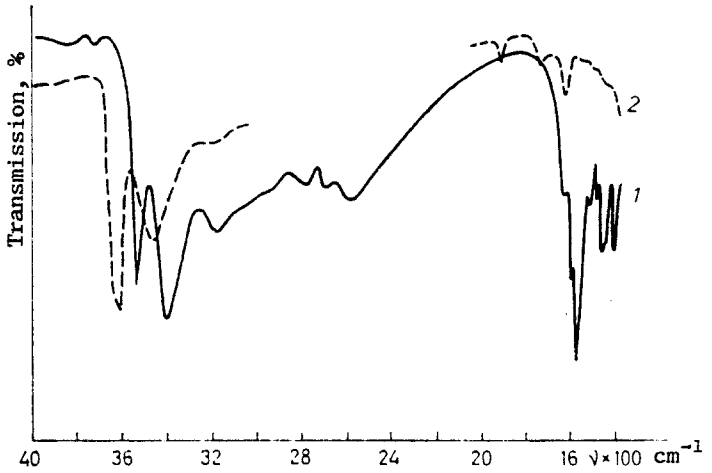

Fig. 1. Infrared absorption spectra of compound (I): a) in tablets with potassium bromide; 2) in chloroform solution (c ~ $1 \cdot 10^{-3}$ M).

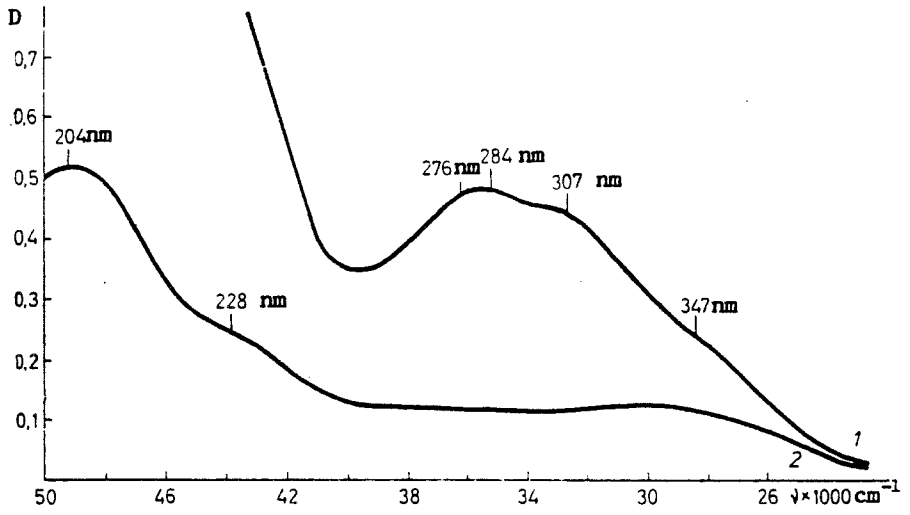

Fig. 2. Electronic absorption spectrum of compound (I) in ethanol: 1) c = $5 \cdot 10^{-5}$ M; 2) c = $1 \cdot 10^{-5}$ M.

It is known [4, 8] that ν_{OH} of the OH forms of pyrazolones in the crystalline state appears in the form of broad bands in the region of 3200-2400 cm^{-1}. In particular, in the spectra of 1-phenylethyl-3-methyl-4-nitropyrazol-5-one and 1-i-butyl-3-phenylpyrazol-5-one, which can be regarded as models of compound (I), the maximum of the ν_{OH} bands appears in the region of 2600-2400 cm^{-1} [8]. Consequently, the broad band can be assigned to ν_{OH} of the pyrazolone ring, which overlaps with ν_{H_2O}, while the small change in the position of its center of gravity in the transition from the crystal to the solution in chloroform indicates that the OH group participates in the formation of a hydrogen bond with the NO_2 group.

Since ν_{NH} cannot be greater than 3450-3470 cm^{-1} [12], the high-frequency band at 3530 cm^{-1} (in potassium bromide) and 3620-3600 cm^{-1} (in chloroform) belongs to ν_{OH} of the substituent at position 3. The change in its position in the transition of (I) from the crystal to the solution indicates that the OH group participates in the formation of intermolecular hydrogen bonds in the crystal. The intramolecular hydrogen bond between the OH group and the N atom at position 2 is absent or is very weak, since the position of ν_{OH} in chloroform solution is practically the same as for the free OH groups of phenol (3600 cm^{-1} [13]).

In view of the foregoing the bands at 3390 cm^{-1} (in potassium bromide) and 3450 cm^{-1} (in chloroform) can be assigned to ν_{NH}, while their shift in the transition from the crystal to the solution indicates that the NH group participates in the formation of intermolecular hydrogen bonds in the crystal.

In the spectrum of compound (I) in acetonitrile solution the ν_{OH} and ν_{NH} bands overlap and form a broad strong approximately symmetrical band with a maximum at 3250 cm^{-1}. Such a form of the band is probably due to the formation of hydro-

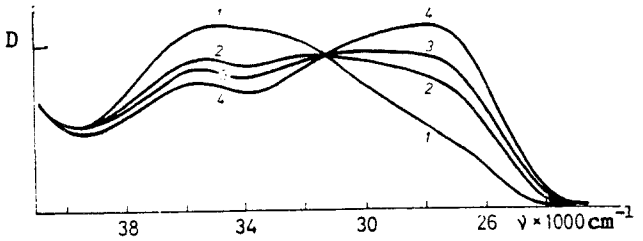

Fig. 3. Effect of the addition of alkali on the electronic absorption spectrum of (I). c = $5 \cdot 10^{-5}$ M (constant): 1 $c_{NaOH} = 0$; 2) $c_{NaOH} = 0.5 \cdot 10^{-5}$; 3) $c_{NaOH} = 1 \cdot 10^{-5}$; 4) $c_{NaOH} = 2 \cdot 10^{-5}$ M.

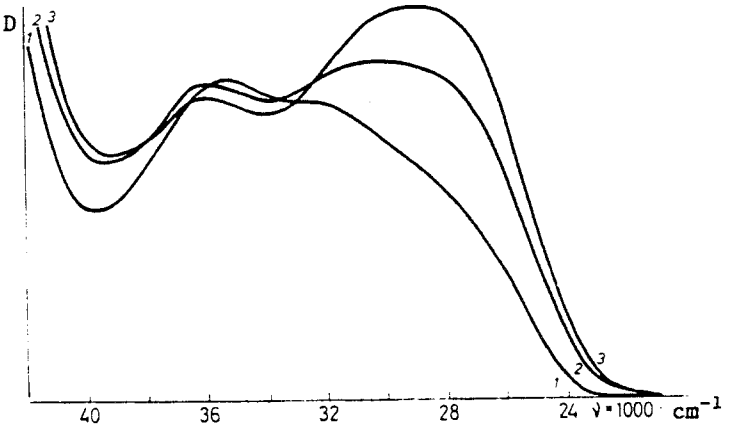

Fig. 4. Effect of the concentration of compound (I) on the position and relative intensity of the bands in the electronic absorption spectrum: 1) c = $8 \cdot 10^{-5}$ M, d = 1 cm; 2) c = $4 \cdot 10^{-5}$ M, d = 2 cm; 3) c = $1.6 \cdot 10^{-5}$ M, d = 5 cm.

gen bonds between the OH and NH groups and the solvent. The presence of the ν_{NH} band in the IR spectra confirms the conclusion that compound (I) exists mainly in forms (Id) or (Ie) under the indicated conditions.

Electronic Absorption Spectra. It was established that one band in the electronic spectrum of pyrazolone with a maximum at ~235 nm corresponds to the OH form, while the presence of a second maximum with $\lambda \approx$ 240-250 nm indicates the presence of the CH and/or NH forms of pyrazolone [4, 5]. The high intensity of the last band in some cases makes it possible to distinguish between the NH and CH forms; the ε value of the absorption bands of the fixed CH forms of pyrazolone amounts to ~4800, while that of the NH forms is approximately twice as large (~9000) [5].

The presence of the NO_2 group at position 4 and Ph–OH at position 3 of the pyrazolone ring must lead, on the one hand, to a shift of the bands of the pyrazolone system and, on the other, to the appearance of new bands.

In the electronic spectrum of (I) in ethanol there are two regions of absorption (Fig. 2). In the short-wave region there is a maximum at 204 nm ($\log \varepsilon$ 4.71) and a clearly defined shoulder at ~228 nm ($\log \varepsilon$ 4.36). In the more long-wave region there is a maximum at 284 nm ($\log \varepsilon$ 3.95), which has shoulders on the short-wave side at ~276 nm ($\log \varepsilon$ 3.949) and long-wave side at 307 nm ($\log e$ 3.92) and a shoulder of comparatively low intensity at $\lambda \sim$ 347-350 nm with $\log \varepsilon \approx$ 3.72. The bands in the regions of 284 and 276 nm most likely belong to the phenol fragment [13, 14]. The absence of absorption bands in the region of 240-250 nm confirms the previous conclusion about the realization of the OH form of compound (I) and corresponds to its NMR and IR spectra.

The shoulder in the region of 347-350 nm in the spectrum of (I) in ethanol solution is complex in nature. On the one hand, it does not disappear completely with the addition of acid (HCl, H_2SO_4) to the ethanol solution (although it decreases in intensity) and appears in solutions in chloroform, toluene, and acetonitrile. On the other hand, as seen from Fig. 3, the intensity of this band increases sharply with the addition of alkali to the ethanol solution. From this it can be concluded that two bands obviously appear in the investigated region: a) A band for the $n-\pi^*$ transition, due to the NO_2 group of the pyra-

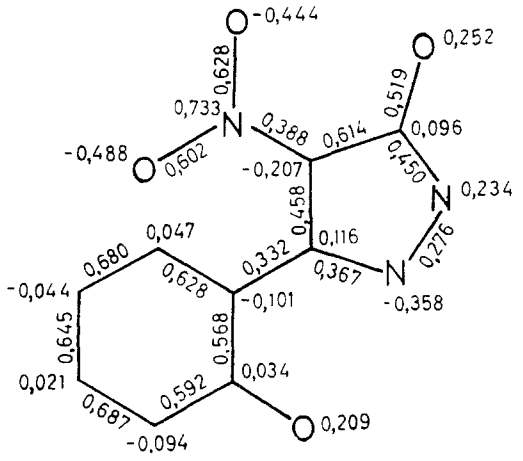

Fig. 5. Molecular diagram of compound (I) in the tautomeric form (Ie) in the ground state. The orders of the π bonds and the π charges at the atoms are given.

TABLE 2. Calculated Electronic Absorption Spectrum of Compound (I)

λ,nm	Oscillator force F	Transitions*	Main electron donors	Main electron acceptor
364,5	0,132	10→11 (86)	—Ph—OH	$—NO_2$
321,9	0,202	9→11 (50); 8→11 (38)	Pr	$—NO_2$
309,2	0,112	10→12 (59); 8→11 (20)	—Ph—OH	Pr, NO_2
290,1	0,126	9→11 (46); 8→11 (29)	—Ph—OH	$—NO_2$
252,4	0,127	8→12 (37); 10→13 (37)		
241,6	0,065	9→12 (46); 8→12 (25)		
223,7	0,004	10→14 (45)		
212,3	0,805	9→12 (30); 10→14 (28); 7→11 (22)		
206,9	1,088	7→11 (53)		
199,9	0,500	9→14 (43)		

*The numbers of the MOs are given (10 HOMO; 11, LUMO), and the contributions (%) are given in parentheses. The transitions whose contributions are greater than 20% are given.

zoline system and analogous with the appearance of the n–π* transition in the region of 330 nm in the spectrum of nitrobenzene compared with the spectrum of unsubstituted benzene [13]; b) a band for the π_f–π* transition in the ionized molecule of the compound (I^-). The relatively high intensity of the absorption in the region of ~350 nm in ethanol solution compared with the solutions in chloroform, toluene, and acetonitrile indicates that the following equilibrium exists in ethanol:

$$I \rightleftarrows I^- + H^+.$$

With the addition of alkali the equilibrium is shifted to the right.

The equilibrium is affected by the concentration of (I) in ethanol and also by the nature of the solvent (polarity and basicity). Thus, with dilution of the solution by approximately four times the intensity of the band at 347-350 nm is increased by approximately twice (Fig. 4), and it becomes stronger than the bands in the region of 276-284 nm. The presence of pseudoisobestic points indicates the presence of at least two forms of the compound, i.e., (I) and (I^-). Thus, the content of the ionized form is increased when the solution of (I) in ethanol is diluted.

It was found by potentiometry that the pK_a value of compound (I) amounts to 3.9 ± 0.1. The ionization of (I) most likely takes place as a result of deprotonation of the OH groups of the phenol and pyrazolone rings. In fact, the pK_a value of phenol is 9.98 [15], the value for pyrazole is 14 [14], and the value for pyrazolones not containing nitro groups in the ring is ~7-8 [16]. The significant decrease of the pK_a value in compound (I) is clearly due to the effect of the nitro group, and it will

have the strongest effect on the OH group at the o position of the heterocycle as follows, in particular, from the IR spectra. A similar effect appears in the transition from phenol to o-nitrophenol, where the pK_a value decreases from 9.98 to 7.23 [13, 17].

In the electronic absorption spectrum of (I) in low-polarity solvents (chloroform, toluene) in the long-wave region there is an absorption band with a maximum at 307-314 nm and shoulders in the regions of 278 and 350-360 nm. The absence of an appreciable hypsochromic shift of the maximum of the band at ~312 nm with increase in the polarity of the solvent and the intensity make it possible to assign it largely to the π–π^* transition. At the same time, the change in the intensity ratio of the bands with maxima at about 276-284 and 312 nm with change in the type of solvent and in the concentration of the solutions makes it possible to suppose that in solutions compound (I) exists in the form of rotational isomers on account of rotation of the substituent at position 3 in relation to the plane of the pyrazolone ring, and the quantitative ratio of the isomers changes with replacement of the solvent or with change in the concentration. Here the band with $\lambda \approx 312$ nm clearly characterizes the planar structure, while the band with $\lambda \approx 276$-284 nm characterizes the structure with rotation of the phenyl substituent in relation to the pyrazolone system.

Calculation of the electronic absorption spectrum of the molecule of (I) [form (Ie)] shows that the long-wave region of the absorption is due to four transitions.

The band which appears in the experimental spectrum in the form of a shoulder at ~350 nm is determined to the extent of 86% by the transition from the HOMO to the LUMO. According to the c_{ij}^2 values, the main contribution to the HOMO comes from the oxygen (26%) and carbon (total 66%) atoms of the substituent at position 3, while the main contribution to the LUMO comes from the atoms of the nitro group (total 74%). The actual transition can be assigned to intramolecular charge transfer from the phenyl substituent to the nitro group. In fact, in the transition from the ground to the first excited state there is a decrease in the π charge at the atoms of the phenyl substituent (total 0.724 $\bar{e}$) and an increase in the charge at the atoms of the nitro group (by 0.634 $\bar{e}$).

An assignment was made for the other bands in the spectrum of the molecule of (I) with respect to the types of transitions with an indication of the main electron donors and acceptors (Table 2). It is seen that the transition with $\lambda \approx 309$ nm is due mainly to the transfer of π-electron density from the phenyl substituent to the pyrazolone system and must, consequently, be particularly sensitive to change in the planar structure of the molecule of (I). This is consistent with the experimental observations described above. A molecular diagram of the π-electron density distribution was obtained for the molecule of (I) in the ground state (Fig. 5).

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrophotometer in the crystalline state and in solutions by standard procedures. The electronic spectra were recorded on Specord UV-vis and Specord M-40 spectrophotometers.

The NMR spectra were recorded on a Bruker WM-400 spectrophotometer at 400 MHz for ^1H and 100.6 MHz for ^{13}C for solutions in CD_3OD (c ~ 20%, T 25°C). The signals in the ^{13}C NMR spectrum of (I) without proton decoupling were assigned in light of their multiplicity. The chemical shifts were determined with reference to TMS.

The quantum–chemical calculation of compound (I) was conducted in the PPP approximation in the Dewar variant by means of the programs and the procedure described in [17].

The acidity of compound (I) was determined by potentiometry according to the previously described procedure [15]. The concentration of (I) in 50% water–ethanol solution was $c_1 = 1 \cdot 10^{-3}$ M, $c_{NaOH} = 1 \cdot 10^{-2}$ M.

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SYNTHESIS AND DEAMINATION OF 9-AMINOIMADAZO[1,2-*a*]BENZIMIDAZOLES

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The reaction between 1,2-diaminobenzimidazole and α-halocarbonyl compounds has given some novel 9-aminoimidazo[1,2-a]benzimidazoles. On treatment with nitrous acid or potassium hydroxide in DMSO, these compounds give, in addition to the deaminated compounds, 3-nitroso-derivatives of the deamination products. In the system DMSO–KOH, 9-benzylideneaminoimidazobenzimidazoles are converted smoothly into 1(9H)-imidazobenzimidazoles. It is shown that 3-nitroso-derivatives which are unsubstituted in the NH group exist predominantly in the hydroxyimino form.

Significant numbers of 9-substituted imidazo[1,2-*a*]benzimidazoles have shown high pharmacological activity [1, 2]. It was therefore of interest to develop a method of synthesis for the hitherto unknown 9-aminoimidazo[1,2-*a*]benzimidazoles. These could clearly be obtained by the reaction between 1,2-diaminobenzimidazole [3] and α-halocarbonyl compounds.

We have found that the diamine (I) reacts readily with α-haloketones to give the salts (II), which on boiling in 2% sodium bicarbonate solution cyclize in 75-80% yields to 9-aminoimidazo[1,2-*a*]benzimidazoles (III). The imines (IV) are undoubtedly intermediates in this reaction, and some of these (IVa, b) were isolated and characterized. On cyclization of the salts (IIc, d), in addition to (IIIc, d) there were obtained 10-12% yields of 1-amino-3-acetonyl- (Vc) and 1-amino-3-pivaloylmethylbenzimidaz-2-one (Vd). On heating in acid, the method normally used for the preparation of 9-alkylimidazo[1,2-*a*]benzimidazoles [4], (II) were unaffected. It is noteworthy that under the conditions of formation of the salts (II), the reaction of 1,2-diaminobenzimidazole with α-bromopropiophenone results in spontaneous cyclization to the imidazobenzimidazole (IIIe), half of the starting diamine binding the hydrogen bromide liberated.

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