

UV-SPECTRAL AND QUANTUM CHEMICAL STUDIES OF DEOXYVASICINONE AND ITS DERIVATIVES

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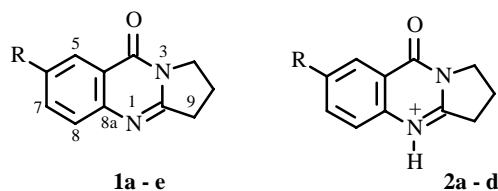
Comparison of the spectral parameters and results of quantum chemical calculations showed that electron-donating substituents in the 6-position of deoxyvasicinone (DOV) direct electrophilic substitution reactions to the 5- and 7-positions, have no influence on the polarization of the C=O bond, and decrease the reactivity (RA) toward reduction of the N1=C2 bond and substitution of the C9 H atom. Protonation of N1 and introduction of a nitro group in the 6-position of DOV changes the direction of the RA of these centers.

Key words: deoxyvasicinone and its derivatives, UV spectra, quantum chemical calculations, reactivity indices.

Deoxyvasicinone (DOV, **1a**) is one of the interesting quinazolinone alkaloids that have been isolated from *Peganum harmala*. DOV and its derivatives are used as raw material to prepare deoxypeganine, which is used in medicine as an anticholinesterase agent [1].

The ability to direct chemical reactions and the design of effective technologies to synthesize new compounds with given properties are made possible by studying the electronic structure of DOV and its derivatives. Reactions at the N atom in the 1-position, C6, C8, the carbonyl on C4, the H atom on C9, and the N1=C2 bond are characteristic of DOV [2-8].

It seemed interesting to investigate the effect of the substituent in the 6-position on the reactivity of DOV. For this, we studied the electronic structure of **1a** and its 6-amino-, -hydroxy-, -methoxy-, and -nitro- derivatives (**1b-e**) using UV spectroscopy and quantum chemistry.



1a: R = H; **1b:** R = NH₂;
1c: R = OH; **1d:** R = OCH₃;
1e: R = NO₂

Table 1 lists the data for the UV spectra of **1a-e**.

The absorption band with a maximum at 265 nm (λ_{\max}), which corresponds to a π -type single-configuration transition, is very sensitive to substituent effects [9, 10].

The bathochromic shift of this band with increasing solvent polarity, i.e., on going from ethanol to methanol, confirms the $\pi-\pi^*$ nature of the transition.

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TABLE 1. UV Spectra of Deoxyvasicinone (**1a**) and Its Derivatives **1b-e**

Compound	Ethanol		Methanol		Compound	Ethanol + HCl (pH~2)		$\Delta\lambda_{\max}$, nm
	λ_{\max} , nm	log ϵ	λ_{\max} , nm	log ϵ		λ_{\max} , nm	log ϵ	
1a	265	4.04	275	4.02	2a	271	3.80	6
1b	285	4.20	300	4.30	2b	293	3.99	8
1c	270	4.11	278	4.20	2c	275	3.82	5
1d	271	4.09	276	4.11	2d	276	3.70	5
1e	324	4.08	330	4.12	-	-	-	

$$\Delta\lambda_{\max} = \lambda_{\max}\mathbf{2a-d} - \lambda_{\max}\mathbf{1a-d}$$

TABLE 2. Proton Affinities (PA) of **1a-e** (kcal/mol)

Compound	$\Delta H_f(B)$	$\Delta H_f(BH^+)$	PA
1a	-6.664	142.819	217.717
1b	-8.671	137.506	221.023
1c	-51.017	97.473	218.710
1d	-44.004	103.545	219.651
1e	-14.818	145.142	207.240

Introducing electron-donating (NH_2 , OH, OCH_3) and electron-accepting (NO_2) substituents in the 6-position of DOV leads to a significant long-wavelength shift of λ_{\max} . The largest bathochromic shift of λ_{\max} in the series **1a-e** (Table 1) is observed for **1e** ($\Delta\lambda_{\max} = 59$ nm). This phenomenon is explained by the more effective interaction of the electron-accepting NO_2 with the π -electrons of the azomethine bond (**1e**) compared with the electron-donating substituents (**1b-d**) based on investigations of UV spectra, dipole moments, and quantum-chemical calculations of benzalidene-*p*-nitroaniline and benzalidene-*p*-dimethylaminoaniline [11, 12].

The long-wavelength shift of λ_{\max} in the spectrum of deoxyvasicinone (**2a**) and its derivatives (**2b-d**) upon acidification by HCl (pH ~ 2) is indicative of protonation of N1 and more effective distribution of electrons upon excitation in cations **2a-d** relative to the corresponding unprotonated species [13].

Based on the $\Delta\lambda_{\max}$ values (Table 1), it can be concluded that charge is redistributed most effectively in **2b** compared with **2c** and **-d**. The lack of basic character for N1 is confirmed by the identical UV spectra for **1e** in neutral and acidic medium (pH ~ 2), where N1 is not protonated. This experimental observation is consistent with the very low proton affinity of **1e** relative to the other DOV derivatives (Table 2). The results obtained based on the UV spectra of **1a-d** are compared with the calculated reactivity indices (RAI).

According to the literature [14], the optimal geometric structure of molecules is best sought using the PM3 quantum-chemical method, which describes well systems with a large number of unsaturated bonds. Data from geometry optimization by nonempirical methods differ little from results obtained by semi-empirical methods, in particular, PM3 [14]. The PM3 method has the smallest uncertainty in calculating physicochemical properties (heats of formation, ionization potentials) of compounds containing C, H, N, and O [15, 16]. Therefore, we performed quantum-chemical calculations using PM3 [17] and ZINDO/S [18, 19] in the program set Hyperchem 6.0 (Hypercube Inc.).

For the RAI, we examined the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (Table 3), which determine the capability of the DOV heterocyclic system for electrophilic or nucleophilic substitution; the population of the P_z -atomic orbital and the bond order, which represent the electron density on the atoms (Table 4) and between two bound atoms (Table 5); and the boundary electron densities (BED), i.e., the squares of the MO dissociation coefficients among the atomic orbitals (C_i^2), which indicate the electrophilic and nucleophilic centers of the compounds (Figs. 1-4) [20-23].

TABLE 3. Boundary Orbital Energies for **1a-e** and Their Cations ($\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$, eV)

Compound	E_{HOMO} , eV		E_{LUMO} , eV		ΔE , eV	
	PM3	Zindo/S	PM3	Zindo/S	PM3	Zindo/S
1a	-8.947	-8.255	-0.563	-0.107	8.384	8.148
1b	-8.408	-7.798	-0.506	-0.087	8.102	7.711
1c	-8.696	-7.975	-0.577	-0.163	8.119	7.812
1d	-8.658	-7.927	-0.527	-0.113	8.131	7.814
1e	-9.596	-8.915	-1.556	-1.732	8.040	7.183
2a	-13.434	-12.408	-5.377	-4.876	8.057	7.532
2b	-11.971	-11.430	-5.132	-4.782	6.839	6.648
2c	-12.854	-11.847	-5.311	-4.880	7.543	6.967
2d	-12.507	-12.381	-5.254	-4.851	7.253	7.530

TABLE 4. Population P_z of Atomic Orbitals (PM3)

AO	Population P_z AO								
	1a	2a	1b	2b	1c	2c	1d	2d	1e
N1	1.262	1.493	1.192	1.461	1.195	1.477	1.195	1.475	1.225
C2	0.926	0.893	0.939	0.916	0.936	0.904	0.935	0.905	0.895
N3	1.664	1.537	1.666	1.560	1.666	1.552	1.666	1.553	1.651
O	1.444	1.348	1.445	1.353	1.440	1.345	1.441	1.347	1.429
C5	0.945	0.910	1.009	1.012	1.001	1.027	0.993	0.972	0.862
C7	0.965	0.915	1.019	1.017	1.053	0.975	1.036	1.020	0.903

TABLE 5. Certain Bond Orders of Compounds **1a-e** and Their Cations (PM3)

Bond	Bond Order								
	1a	2a	1b	2b	1c	2c	1d	2d	1e
N1-C2	0.843	0.688	0.848	0.713	0.848	0.703	0.847	0.704	0.819
C2-N3	0.421	0.630	0.410	0.596	0.412	0.611	0.413	0.609	0.453
C4-O	0.816	0.875	0.814	0.872	0.817	0.877	0.817	0.876	0.826
C8a-N1	0.347	0.290	0.344	0.291	0.341	0.285	0.342	0.285	0.376

Introducing electron-donating substituents into the 6-position of the DOV benzene ring raises the level of the HOMO (Table 3) and lowers ΔE of **1b-e** compared with **1a**. The RAI data characterize the increase of π -electron density of the heterocyclic system by the electron-donating substituents. The highest HOMO energy and lowest ΔE ($\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$, eV) of **1b** indicates that charge transfer is most effective from the amino group to the heterocyclic system [13].

On the other hand, the increased population on C5 (Table 4, **1b**, 1.009; **1c**, 1.001; **1d**, 0.993) and C7 (**1b**, 1.019; **1c**, 1.053; **1d**, 1.056), the reduced C8a–N1 bond order (Table 5, **1b**, 0.344; **1c** and **1d**, 0.341±1), and the π -electron density on N1 (Table 4, **1b**, 1.192; **1c** and **1d**, 1.195) in compounds **1b-d** compared with the corresponding RAI of DOV (see Tables 4 and 5) indicate that NH_2 , OH, and OCH_3 substituents of the DOV benzene fragment are donors. The benzene ring has been shown to be more capable of electrophilic substitution at C5 and C7 for compounds **1b-d** than for DOV [24]. The identical C4=O bond order (Table 5) and π -electron density on the O atom (Table 4) in compounds **1a-d** precludes any effect of the NH_2 , OH, and OCH_3 substituents on the C4=O electronic structure. The lack of delocalization of the unshared electron pair (UEP) of N3 into the N1=C2 azomethine bond is evident in the increased π -electron density on N3 and C2 and the increased localized nature of the N1=C2 bond in compounds **1b-d** relative to **1a**.

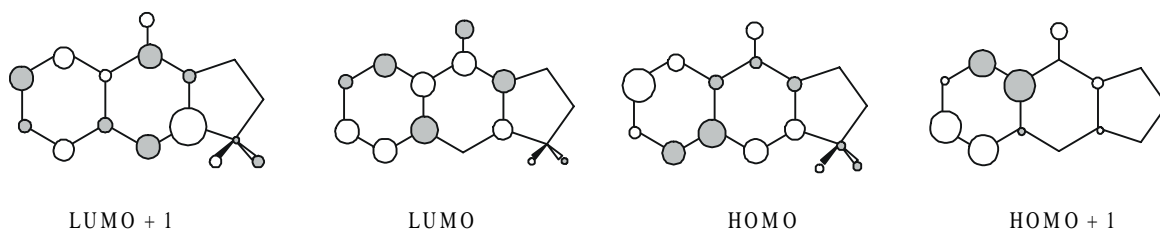


Fig. 1. Distribution of π -electron density in boundary orbitals of molecule **1a** (ZINDO/S). Shaded circles have positive coefficients. The magnitude of the coefficient is proportional to the circle size.

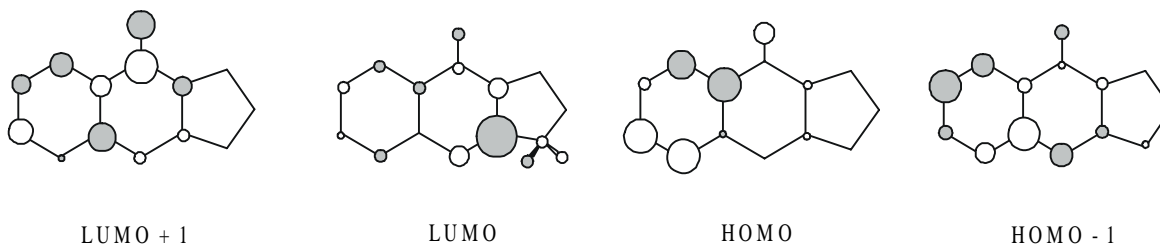


Fig. 2. Distribution of π -electron density in boundary orbitals of molecule **2a** (ZINDO/S).

The π -electron density distribution upon introducing electron-donating substituents into the 6-position decreases the polarization and reduces the reactivity (RA) upon reducing the N1=C2 bond and weakens the mobility of the H atoms on C9 in substitution reactions [2].

The very large lowering of the LUMO level (Table 2, **1e**, 1.556 eV; **1a**, 0.563; **1b**, 0.506; **1c**, 0.577; **1d**, 0.527) indicates that the NO₂ group is electron-accepting center in **1e**. The very low ΔE (Table 3, **1e**, 8.040 eV) relative to the RAI of **1b-e** (see data in Table 3) characterizes the more effective conjugation of NO₂ compared with NH₂, OH, and OCH₃ to the π -electrons of the heterocyclic system [25]. The increased π -electron density on C6 (Table 4, **1e**, 1.196), the C8–N1 (Table 5, **1e**, 0.376) and C2–N3 (Table 5, **1e**, 0.453) bond orders, and the reduction of AO populations (P_Z) of N3 (Table 4, **1e**, 1.651), N1 (**1e**, 1.225), C2 (**1e**, 0.895), C5 (**1e**, 0.862), and C7 (**1e**, 0.903) in **1e** compared with DOV (see Tables 4 and 5) confirms that charge is transferred from N3 to the oxygen atoms of the nitro group of compound **1e** (direct polar conjugation effect [20, 25]). This explains the ability to carry out the Vilsmeier—Haack reaction for the six- and seven-membered analogs of 6-nitro-DOV. It should be noted that this reaction does not occur with unsubstituted seven-membered homologs of DOV [24].

The distribution of π -electron density in the boundary LUMO and HOMO orbitals of molecules **1a** (Fig. 1) and **1e** (Fig. 4) agrees with this conception.

Introducing the electron-accepting NO₂ group in the 6-position of DOV significantly increases the electron deficit on C2 (like for **2a-d**), facilitating the cleavage of the proton from C9 [26].

The deficit of π -electron density of the heterocyclic system of **1e** lowers the polarization of the C=O bond and the π -electron density on the oxygen atom of the carbonyl relative to **1a-d** (see Tables 4 and 5). It is known that the amide carbonyl of **1e** can be reduced only after first reducing the nitro [24].

The lower ΔE in the cations **2a-d** relative to **1a-d** (see Table 3) characterize the more effective change of charge distribution upon excitation in cations **2a-d** compared with the unprotonated species [13]. The reduced population of the P_Z atomic orbitals of C6 (Table 4, **2a**, 0.947; **2b**, 0.931; **2c** and **-d**, 0.891 \pm 3) and N3 (**2a**, 1.537; **2b**, 1.560; **2c** and **-d**, 1.552 \pm 1) and the N1=C2 bond order (see Tables 4 and 5) upon increasing the π -electron density on N1 (Table 4, **2a**, 1.493; **2b**, 1.461; **2c** and **-d**, 1.477 \pm 2) and the N3–C2 bond (Table 5, **2a**, 0.630; **2b**, 0.713; **2c** and **-d**, 0.703 \pm 1) compared with **1a-d** indicates that charge is transferred intramolecularly from the benzene ring and N3 to the ⁺N1H acceptor center.

Molecular diagrams showing the distribution of π -electron density of the boundary orbitals (Fig. 1, **1a**; Fig. 2, **2a**; Fig. 3, **2b**) indicate that atom C2 makes a significant contribution to the formation of the LUMO upon protonating N1 of DOV and its derivatives **2b-d**.

Thus, the electron-accepting properties of ⁺N1H in compounds **2a-d** will help to increase the RA of the N1=C2 bond toward reduction and substitution of the C9 H atom, for example, in bromation [1, 27] and formylation [28, 29] reactions.

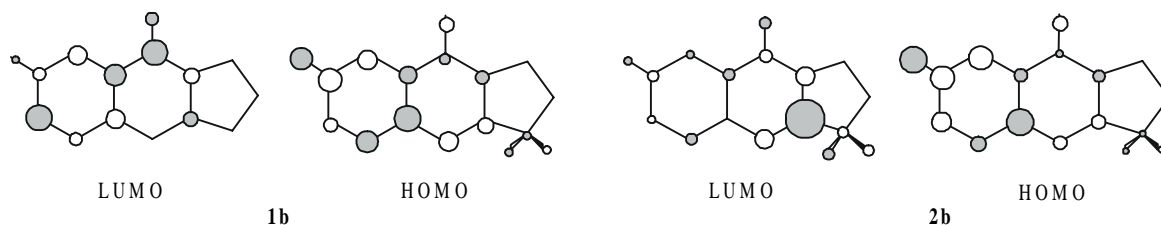


Fig. 3. Distribution of π -electron density in boundary orbitals of **1b** and **2b** (ZINDO/S).

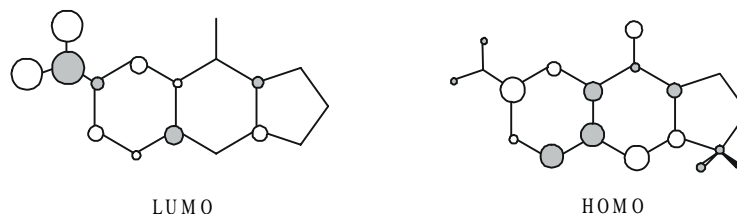


Fig. 4. Distribution of π -electron density in boundary orbitals of molecule **1e** (ZINDO/S).

Furthermore, protonation of N1 increases the C4=O bond order (Table 4) and markedly decreases the π -electron density on the oxygen of the carbonyl (Table 4) and thereby increases the stability of the C4=O bond to reduction in compounds **2a-d** relative to **1a-d** [2].

Comparison of the spectral data and quantum-chemical calculations indicates that electron-donating substituents in the 6-position of DOV increase the nucleophilicity of the benzene ring, creating a preferred direction for electrophilic substitution toward C5 and C7; do not affect the polarization of the C=O bond; and decrease the RA toward reduction of the N1=C2 bond and the capability of the C9 H for substitution.

Protonation of N1 and introduction of electron-accepting NO₂ in the 6-position of DOV activates the electrophilicity of C5 and C7, the reduction of the N1=C2 bond, and substitution of the C9 H atom, and decreases the RA toward reduction of the C=O bond.

EXPERIMENTAL

UV spectra were recorded on a Perkin—Elmer Lambda-16 instrument in ethanol and methanol at concentrations $5 \cdot 10^{-5}$ – $5 \cdot 10^{-4}$ M. The accuracy of the absorption maximum determination was ± 0.5 nm; of the extinction coefficient, $\pm 5\%$.

Proton affinities were calculated using the PM3 method and the equation [30]:

$$\text{RA (kcal/mol)} = 367.2 + \Delta H_f(\text{B}) - \Delta H_f(\text{BH}^+),$$

where 367.2 is the enthalpy of formation of H⁺, $\Delta H_f(\text{B})$ is the heat of formation of the molecule, and $\Delta H_f(\text{BH}^+)$ is the heat of formation of the cation.

REFERENCES

1. E. O. Oripov, Kh. M. Shakhidoyatov, Ch. Sh. Kadyrov, and N. D. Abdullaev, *Khim. Geterotsikl. Soedin.*, 684 (1979).
2. Kh. M. Shakhidoyatov, *Quinazolones-4 and Their Biological Activity* [in Russian], Fan, Tashkent (1988).
3. Kh. M. Shakhidoyatov and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 668 (1977).
4. Kh. M. Shakhidoyatov, A. Irisbaev, and N. P. Abdullaev, *Plant Growth Regulators and Herbicides* [in Russian], Fan, Tashkent (1978).

5. Kh. M. Shakhidoyatov, A. Irisbaev, L. M. Yun, E. Oripov, and Ch. Sh. Kadyrov, *Khim. Geterotsikl. Soedin.*, 1564 (1976).
6. Kh. M. Shakhidoyatov, A. Irisbaev, E. Oripov, and Ch. Sh. Kadyrov, *Khim. Geterotsikl. Soedin.*, 557 (1976).
7. G. A. Belova and Kh. M. Shakhidoyatov, *Khim. Prir. Soedin.*, 659 (1990).
8. Y. Barakat, Candidate Dissertation in Chemical Sciences, Tashkent (1999).
9. A. V. Luzanov, *Usp. Khim.*, **49**, 2086 (1980).
10. R. N. Nurmukhamedov and N. A. Vasilenko, *Zh. Fiz. Khim.*, **48**, 3053 (1975).
11. A. E. Obukhov, *Zh. Fiz. Khim.*, **69**, 1015 (1995).
12. V. D. Bezuglii, ed., *Azomethines. Structure, Properties, Application*, Izd. Rost. Univ., Rostov-on-Don (1967).
13. Yu. B. Vysotskii, *Opt. Spektrosk.*, **44**, 1025 (1978).
14. A. V. Pogrebnyak, D. A. Konovalov, and V. A. Chelombitko, *Materials of the 55th Regional Conference on Pharmacy, Pharmacology, and Training* [in Russian], Pyatigorsk (2000), p. 39.
15. A. N. Pankratov, *Zh. Strukt. Khim.*, **41**, 696 (2000).
16. M. J. S. Dewar, C. Jie, and J. Yu, *Tetrahedron*, **49**, 5003 (1993).
17. J. J. P. Stewart, *J. Comp. Chem.*, **10**, 221 (1989).
18. J. Ridley and M. C. Zerner, *Theor. Chim. Acta*, **32**, 111 (1973).
19. C. Forber and M. C. Zerner, *J. Am. Chem. Soc.*, **107**, 5884 (1985).
20. L. A. Yanovskaya, *Modern Theoretical Principles of Organic Chemistry* [in Russian], Khimiya, Moscow (1978).
21. V. F. Traven', *Electronic Structure and Properties of Organic Molecules* [in Russian], Khimiya, Moscow (1989).
22. E. A. Gastilovich, V. G. Klimenko, N. V. Korol'kova, and R. N. Nurmykhametov, *Usp. Khim.*, **69**, 1128 (2000).
23. M. Karelson, V. S. Lobanov, and A. R. Katritzky, *Chem. Rev.*, **96**, 1027 (1996).
24. Kh. M. Shakhidoyatov, Doctoral Dissertation in Chemical Sciences, Moscow (1983).
25. V. I. Minkin, *Zh. Fiz. Khim.*, **41**, 556 (1967).
26. I. F. Tupitsyn, S. A. Egorov, and A. Yu. Shibaev, *Zh. Obshch. Khim.*, **61**, 1822 (1991).
27. Kh. M. Shakhidoyatov, E. Oripov, A. Irisbaev, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 825 (1976).
28. V. Purnaprajna and S. Seshadri, *Indian J. Chem., Sect. B*, **15**, 109 (1977).
29. R. S. Pandit and S. Seshadri, *Indian J. Chem., Sect. B*, **11**, 532 (1973).
30. V. K. Turchaninov, A. I. Vokin, L. V. Baikalova, and A. M. Shulunova, *Zh. Obshch. Khim.*, **70**, 627 (2000).