QUANTUM-CHEMICAL INVESTIGATION OF DEOXYPEGANINE AND ITS SALTS

I. PHOTOCHEMICAL OXIDATION OF DEOXYPEGANINE

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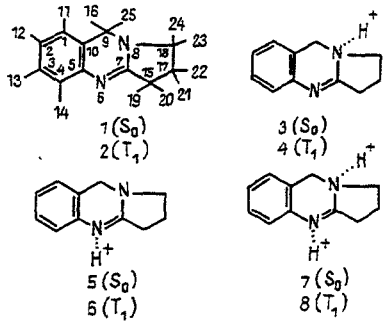
Hypothetical models of the interaction of deoxypeganine molecules with a solvent have been considered by the MO LCAO quantum-chemical method in the AM1 approximation. Excited triplet states of deoxypeganine and its analogues have been calculated by the method of molecular interactions. A free-radical mechanism of photochemical oxidation has been proposed on the basis of the results obtained and of literature information.

It has been reported previously that peganine (vasicine) and its analogues undergo photochemical oxidation [1, 2] which takes place at different rates in solvents of different natures. Thus, oxidation in aqueous alcohol is considerably retarded and in methanol it takes place very feebly, while in the nonpolar aprotic toluene it is rapid (after UV irradiation for 3 h, more than 22% of the main substance is oxidized) [2]. The oxidation of deoxypeganine (DOP) in organic solvents on irradiation takes place similarly [3, 4].

In connection with the fact that in protonic solvents the formation of hydrogen bonds between the molecules of a substance and the solvent is characteristic, we have considered protonated DOP molecules in the ground and excited states.

It is known that in the singlet state the lifetime of an excited molecule is very short and is insufficient for the formation of the necessary conditions for an oxidative process, while for the triplet state the lifetime of a molecule corresponds to the usual rate of an oxidation reaction [5]. In general, hypothetical structures can be described in the form of eight schemes of the ground (S_0) and excited (T_1) states of molecules where a proton is taken as the initiating agent and all possible variants of its inteaction with the DOP molecule are taken.



In order to calculate the electronic structures of systems 1–8 with the aim of finding the direction and mechanism of the oxidation reaction, we used the MO LCAO quantum-chemical method in the AM1 approximation [6]. The calculations were performed by the AMPAC program on a personal computer of the PC/AT 386 type with complete optimization of all the geometric parameters.

Analysis of the distribution of the charges on the atoms showed that the oxidative process can take place only at the C_9 center, where in the ground structure of DOP and its excited states the magnitude of the charge amounts to 0.05 e and 0.03 e (Table 1). At the

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TABLE 1. Charge Distribution on the Atoms of the DOP Molecule, e

Atom	1	2	3	4	5	6	7	8
C_1	−0,11	−0,11	−0,09	−0,08	−0,09	−0,10	−0,07	−0,09
C_2	−0,15	−0,15	−0,08	−0,04	−0,10	−0,07	−0,02	0,04
C_3	−0,12	−0,15	−0,11	−0,11	−0,09	−0,06	−0,09	0,02
C_4	−0,11	−0,07	−0,08	−0,08	−0,12	−0,16	−0,03	−0,18
C_5	0,03	−0,07	−0,06	0,08	0,01	0,06	0,11	0,17
N_6	−0,22	−0,07	−0,02	−0,09	−0,20	0,06	−0,02	−0,11
C_7	0,13	−0,06	−0,02	−0,12	0,23	−0,08	0,10	−0,09
N_8	−0,34	−0,23	−0,03	0,03	−0,21	−0,18	−0,01	−0,02
C_9	0,05	0,03	−0,07	−0,07	−0,01	0,00	−0,09	−0,10
C_{10}	−0,14	0,14	−0,14	−0,19	−0,12	−0,11	−0,12	−0,09
C_{15}	−0,12	−0,09	−0,12	−0,10	−0,15	−0,10	−0,16	−0,12
C_{17}	−0,18	−0,17	−0,18	−0,18	−0,18	−0,17	−0,19	−0,18
C_{18}	−0,01	0,02	−0,12	−0,13	−0,04	−0,03	−0,11	−0,12
H_{11}	0,13	0,12	0,16	0,16	0,16	0,18	0,19	0,20
H_{12}	0,13	0,13	0,17	0,17	0,17	0,17	0,21	0,22
H_{13}	0,13	0,13	0,17	0,18	0,17	0,17	0,21	0,22
H_{14}	0,15	0,14	0,18	0,19	0,16	0,17	0,19	0,21
$H_{16}(O_{16})$	0,08	0,11	0,15	0,14	0,13	0,16	0,19	0,19
H_{25}	0,08	0,11	0,15	0,16	0,13	0,16	0,18	0,19
H_{19}	0,12	0,16	0,15	0,15	0,15	0,12	0,19	0,17
H_{20}	0,12	0,11	0,15	0,16	0,15	0,13	0,19	0,18

same time, several centers (C_2—C_4, C_{15}, and C_{17}) with increased electron density are favorable for electrophilic attack.

The low electron density at C_9 in the unprotonated structures 1 and 2 and the appreciable lowering of the energy of the bonds of C_9 with H_{16} and H_{25} on the excitation of the molecule indicate that in a photochemical process the protons at C_9 are more susceptible to detachment than to substitution. However, in the hypothetical protonated structures the electron density at C_9 is increased and therefore the detachment of the H_{16} and H_{25} atoms from it is hindered (Tables 1 and 2).

Thus, on the basis of an analysis of the calculated and experimental results it may be concluded that the DOP molecule is more stable in protonated than in aprotic solvents and that the oxidation process itself takes place through a free-radical mechanism [7], a necessary condition for this being the passage of the molecule into the excited triplet state, DOP (T_1). Then, under the action of light, the excited molecule loses a proton and forms a radical, which, in its turn, reacts with atmospheric oxygen to give a peroxy radical. After this, the process continues in a similar way to the scheme of radical autooxidation.

In the case of deoxyvasicinone, the oxidation product of DOP, the carbonyl group is conjugated with a fairly large π-electron system which, in the lowest π,π*-triplet state leads to the greatest increase in the negative charge on the oxygen atom. The deoxvasicinone

TABLE 2. Energies of Some Bonds of DOP and Its Protonated Analogues in the Ground and Excited States

Bond	1	2	3	4	5	6	7	8
E (1—11)	−12,565	−12,560	−12,542	−12,499	−12,508	−12,514	−12,422	−12,305
E (2—12)	−12,617	−12,625	−12,493	−12,408	−12,521	−12,453	−12,206	−12,152
E (3—13)	−12,573	−12,613	−12,517	−12,515	−12,494	−12,545	−12,406	−12,229
E (4—14)	−12,562	−12,508	−12,419	−12,417	−12,549	−12,602	−12,360	−12,578
E (9—16)	−11,956	−11,714	−12,140	−11,978	−11,909	−11,621	−12,062	−12,052
E (9—25)	−11,958	−11,718	−12,035	−11,918	−11,865	−11,614	−12,043	−11,848
E^*_{av}(C—H)	−12,20	−12,168	−12,225	−12,193	−12,210	−12,168	−12,18	11,850* 12,192** 12,191*

*The mean value of the energies of the C—H bonds of the five-membered ring is given.
**The mean value of the energies of the C—H bonds at C_{15}, C_{17}, and C_{18} is given.

molecule is therefore stable in the lowest π,π^*-triplet state and is reduced only by strong H-donors.

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INTRAMOLECULAR CYCLIZATION OF ortho-(CYCLOHEX-2-ENYL)ANILINES

SYNTHESIS OF ELLIPTICINE

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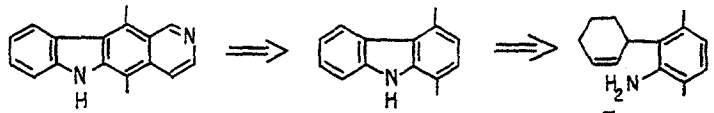
A convenient method is proposed for the synthesis of the alkaloid ellipticine, which possesses a pronounced antitumoral activity. The interaction of 3-bromocyclohexene (1 equiv.) and 2,5-xylylidine (4 equiv., 150°C, 5 h) gave a mixture of hexa- and tetrahydrocarbazoles which was dehydrogenated in the presence of Pd/C to the key synthon 1,4-dimethylcarbazole. The formylation of the carbazole by the Vilsmeier-Haack reaction, interaction with 2,2-diethoxyethylamine, and reduction of the imine formed over Raney nickel led to 3-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole, the boiling of the N-tosylate of which gave ellipticine in high yield.

The alkaloid ellipticine (I), isolated from the leaves of the plant Ochrosia elliptica Gabil (fam. Apocynaceae) [1], and some of its synthetic analogues possess a high antitumoral activity [2, 3]. In view of this, several methods for synthesizing ellipticine and its derivatives based on traditional methods have been developed [4, 5].

A retrosynthetic analysis of the structure of ellipticine (I) has enabled a convenient approach to the synthesis of the alkaloid to be discovered. We have previously realized a fairly simple route using ortho-(cyclohex-2-enyl)-2,5-xylidine (III), the cyclization of which, followed by dehydrogenation, led to 1,4-dimethylcarbazole (II) – the key compound in the synthesis of ellipticine (I) [6].



I II III

The Claisen rearrangement of N-alkenylarylamines that has been developed over a number of years and the intramolecular cyclization of N- and C-alkenylarylamines form a promising

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