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SYNTHETIC ANALOGS OF *Peganum* ALKALOIDS
VIII. A QUANTUM-MECHANICAL INVESTIGATION OF THE REDUCTION OF DEOXYPEGANINE AND ITS DERIVATIVES

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The alkaloid deoxypeganine and some of its derivatives have been subjected to reduction with sodium tetrahydroborate and with the complex $NaBH_4 \cdot BF_3 \cdot Et_2O$. It has been shown that the structures of the reduction products depend on the presence and positions of substituents in the benzene ring. The quantum-chemical calculations performed have confirmed the probable formation of reduced structures of the type of o-aminobenzylpyrrolidine and the type of a macrocyclic diamine.

In investigations published previously on the reduction of the quinazolone and quinazoline alkaloids of *Peganum harmala* with sodium tetrahydroborate in an alcoholic medium it was shown that these alkaloids behave differently. The quinazolone alkaloids form dihydro products with reduction of the C=N double bond and retention of the carbonyl group [1—3], while the quinazoline bases give tetrahydroderivatives with the structures of *ortho*-aminobenzylpyrrolidines [1, 4]. Sengupta et al. [5], who used for the reduction of amines an effective new reagent consisting of a combination of sodium tetrahydroborate with the ether complex of boron trifluoride, ascribed the structure of a cyclic diamine (**7**) to the reaction product from 6-methoxydeoxyvasicinone (**12**). Thus, the question arises of an alternative structure for the tetrahydro derivatives and of the influence of the substituents and the reducing agents on the course of the process described.

In order to solve this problem, we reduced the quinazoline bases deoxypeganine (**1**), 5-methoxydeoxypeganine (**2**), and 6-bromodeoxypeganine (**3**) with sodium tetrahydroborate, leading to the tetreahydro derivatives (**4—6**). Then, starting from the corresponding quinazolone analogs deoxyvasicinone (**8**), 5-methoxydeoxyvasicinone (**9**), and 6-bromodeoxyvasicinone (**10**), by using the complex $NaBH_4 \cdot BF_3 \cdot Et_2O$ as in [5] we synthesized tetrahydro compounds that proved to be identical with compounds (**4—6**). Their structures were deduced from their spectral characteristics [1].

Our experiments confirmed that the complex $NaBH_4 \cdot BF_3 \cdot Et_2O$ is a more effective reducing agent than sodium tetrahydroborate. When the latter is used, compounds (**4—6**) are obtained in two stages: first the quinazolone bases (**8—10**)are reduced with zinc in an acid medium to the quinazolines (**1—3**) [6]. Then the tetrahydro derivatives (**4—6**) are obtained with the use of $NaBH_4$. When the reagent $NaBH_4 \cdot BF_3 \cdot Et_2O$ is used, however, the quinazolone compounds (**8—10**) give the *o*-aminobenzylpyrrolidines (**4—6**) directly. All the transformations described are illustrated in the scheme given below.

We must mention the unusual behavior of 8-methoxydeoxyvasicinone (**11**) under the conditions of the reaction being studied. When it was reduced by the method of Sengupta et al. [5] the dihydro product (**16**) was formed, with retention of the carbonyl group. In this case we did not detected any *ortho*-aminobenzylpyrrolidine. As stated above, deoxyvasicinone (**8**) and its analogs substituted in the benzene ring (**9**, **10**, and **12**) are hydrogenated similarly, giving compounds (**13—15**, and **17**). However, this takes place with the use of ordinary sodium tetrahydroborate.

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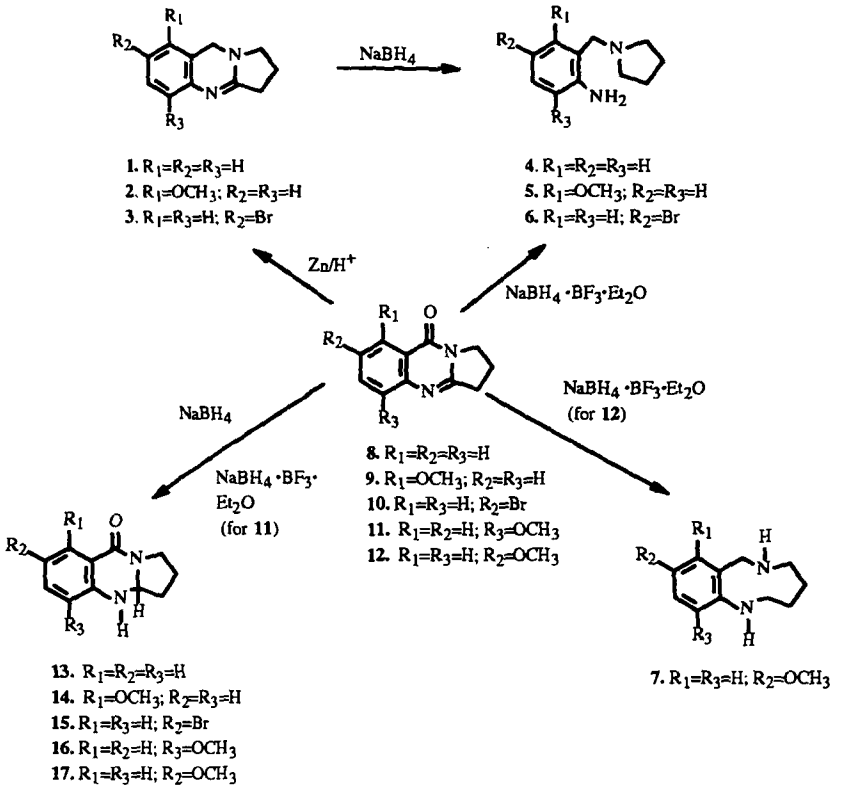


The formation of substance (**16**) was confirmed by spectral studies. Characteristic for it was a shift of the absorption band of the carbonyl group in the IR spectrum to 1645 cm^{-1} in place of the 1680 cm^{-1} for the initial compound. The stretching vibrations of an NH group appeared in the region of 3250 cm^{-1}. In the PMR spectrum there were the signals of the proton in the second position (4.95 pm) and of a secondary amino group (4.88 ppm). At the same time, the characteristic downfield shift of the signal of the H-5 proton (7.83 ppm) was preserved.

Taking into account the formation of compound (**16**) and also the results of [5], we assume that the structure of the products of reduction of the quinazolone bases by the complex $NaBH_4 \cdot BF_3 \cdot Et_2O$ depends on the presence and positions of substituents in the benzene ring.

Unfortunately, the spectral characteristics for reduction products of the type of *o*-aminobenzylpyrrolidine (**4—6**) and for the type of the cyclic diamine (**7**) are fairly close, and it is therefore difficult to give an unambiguous answer to the question of the structure of the compounds obtained. For this reason, in order to attempt to answer it we had recourse to the methods of quantum chemistry.

For the quantum-chemical modeling of the reduction reaction we selected deoxypeganine (DOP) as the simplest of compounds under consideration in the structural respect while at the same time retaining the main properties of more complex compounds. The reduction products (**4**) and (**18**) (see below) are isomers with heats of formation of 56.65 and 14.12 kcal/mole, respectively. However, their great structural differences exclude the existence of a transition state (TS) between them, as was confirmed by a direct search for a TS (energy barrier of the order of 680 kcal/mole) and excluded the reaction scheme DOP + 4H → TS → (**4**) + (**18**). Such energetics of the bonds of (**4**) and (**18**) is confirmed by their close spectral characteristics.

The addition of a hydride radical to DOP takes place at N_1 and C_2 in the heterocycle with cleavage of the double bond and the formation of a radical [7]. Since, from the energetic point of view the addition of a hydride radical at N_1 is more favorable (by 14.78 kcal/mole), we performed calculations of this pathway (Fig. 1). On its approach to a molecule of the reagent the hydride radical overcomes a potential barrier of 4.38 kcal/mole and reaches the bottom of the potential trough of 38.48 kcal/mole at a distance of 0.994 Å, which corresponds to the equilibrium configuration of the radical formed. An increase in the energy of formation of the N—H bond (Fig. 2) takes place linearly up to the potential barrier and then exponentially; the steepest section of the exponent corresponds to an accumulation of charge in the region between the attacking radical and the DOP molecule, which favors the formation of a bond [8] (it is just here, too, that the potential barrier is found).

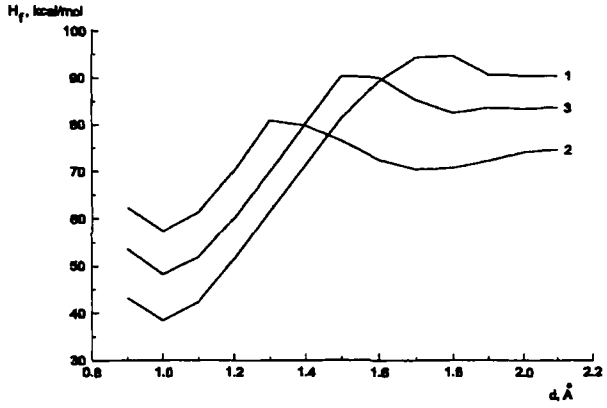


Fig. 1. Reaction pathways on the attack of a hydride radical: *1*) at N_1 of DOP; *2*) at N_3 of the intermediate; *3*) at N_1 of the intermediate.

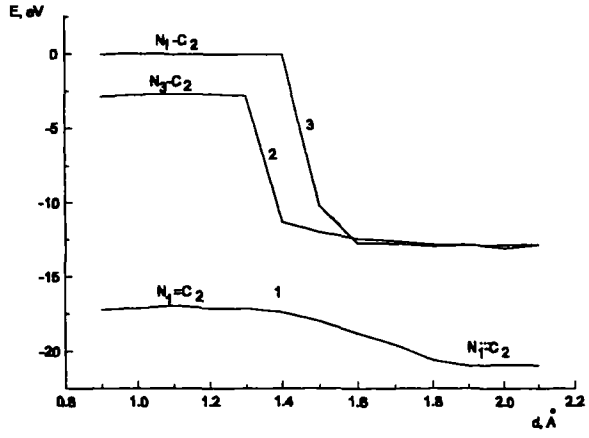
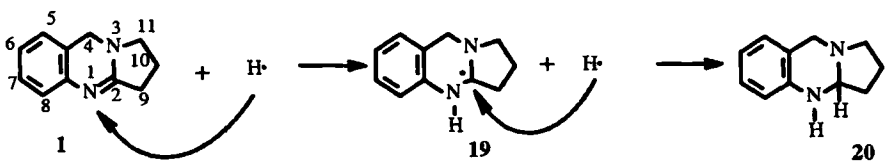


Fig. 2. Energy of the bonds on the attack of a hydride radical: *1*) at N_1 of DOP; *2*) at N_3 of the intermediate; *3*) at N_1 of the intermediate.

On the approach of H˙ to the nitrogen atom, the C=N double bond is weakened to a value of -17.15 eV and is delocalized between the neighboring carbon atoms. There is an increase in the positive change on N_1 (Fig. 3) and in the negative charge on C_2, which subsequently becomes the object of electrophilic attack and adds the following proton, giving the intermediate (**20**) with a heat of formation of 18.54 kcal/mole. Thus, in the first stage of the reaction an intermediate is obtained by the following mechanism:



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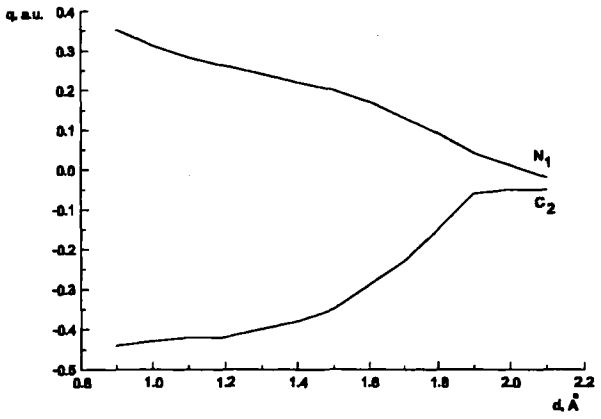
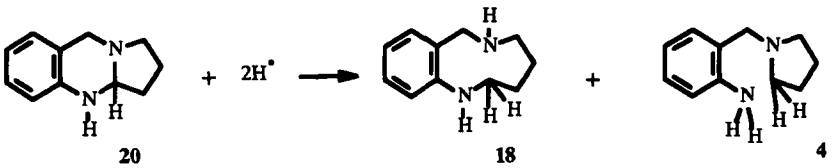


Fig. 3. Dynamics of the charge distributions in the attack of a hydride radical at N_1 of DOP.

We may note that compound (**20**) has been obtained in the reduction of DOP by palladium on carbon [9]. The angle between the six-membered and the five-membered rings of the intermediate, of the order of 114°, makes both the N_1 and the N_3 heteroatoms accessible to further attack and C_2 completely inaccessible as a result of steric hindrance. This fact determines two reaction pathways: with the formation of a macrocycle and with cleavage of the N_1—C_2 bond. The addition of the hydride radical at N_3 (see Fig. 1) passes through a potential barrier of 10.38 kcal/mole, and the radical formed reaches an energy of formation of 57.16 kcal/mole with an equilibrium distance of 0.997 Å. At a distance of approximately 1.3—1.4 Å the C_2—N_3 bond undergoes cleavage (see Fig. 2) and a macrocycle is formed. A largely similar picture is observed on the attack of the hydride radical at N_1 (see Fig. 1). The magnitude of the potential barrier is practically the same, and the equilibrium conformation has a heat of formation of 48.06 kcal/mole at a H—N_1 distance of 1 Å; cleavage of the N_1—C_2 bond takes place at 1.4—1.5 Å (see Fig.2). On the basis of the quantum-chemical calculations discussed above, it may be assumed that during the reaction the two products (**4**) and (**18**) are formed by the following scheme:



The quantum-chemical results obtained are in good agreement with the experimental results (existence of stable intermediate and of two reaction products) and confirm earlier theoretical investigations in the field of the class of reactions considered (for example, K. Fukui [10]).

EXPERIMENTAL

General Observations. IR spectra were recorded on a Perkin-Elmer model 2000 Fourier spectrometer; mass spectra on a MKh-1321 spectrometer; and PMR spectra on a Tesla BS 567 instrument. Chromatographic monitoring was conducted on silica gel plates in the chloroform—benzene—methanol (4:5:0.5) and ethyl acetate—methanol—ammonia (19:1:0.1) systems.

The quinazoline bases (**1**—**3**) were obtained from the corresponding quinazolones (**8**—**10**) by reduction with zinc in hydrochloric acid [11].

Quantum-chemical calculations were performed with the aid of the MNDO92 program [12] and the MOPAC7 program in the PM3 approximation [13].

Synthesis of the Aminobenzylpyrrolidines (4—6). a) Solutions of the bases (**1—3**) in ethanol were treated with $NaBH_4$ in portions, and the mixtures were heated for 3 h. The solvent was evaporated off, the residues were treated with 5% HCl, and the resulting solutions were washed with chloroform, made alkaline with conc. NH_4OH, and extracted with chloroform. The organic extracts were washed with water, dried with Na_2SO_4 and evaporated.

b) In drops, 2 ml of a freshly prepared solution of boron trifluoride etherate in 5 ml of tetrahydrofuran was added to a mixture of 0.3 g of 6-bromodeoxyvasicinone (**10**), 15 ml of tetrahydrofuran, and 0.3 g of $NaBH_4$. The reaction mixture was boiled for 5 h and then the solvent was distilled off; 5% HCl solution was added to the residue to give an acid reaction and the mixture was heated on the water bath for 1 h. After cooling, it was carefully alkalinized and was treated with chloroform. The chloroform solution was washed with water and dried with Na_2SO_4. Evaporation of the solvent yielded 0.28 g of product, which was recrystallized from hexane. The melting point of 68—69°C underwent no depression in a mixture with the substance synthesized by method a).

Base (4). Oil. IR: 3431, 3294, 3023, 2964, 2928, 2874, 2797, 2733, 2360, 1616, 1493, 1459, 1374, 1374, 1328, 1285, 1201, 1135, 1120, 1068, 1034, 986, 944, 879, 749, 634, 537, 444.

Mass (*m/z*): 176(M^+), 159($M-NH_3$)$^+$, 147, 134, 107, 106, (M-70)$^+$, 84, 70.

PMR ($CDCl_3$, HMDS): 1.68 (4H, m, H-3′, H-4′); 2.35 (4H, m, H-2′, H-5′); 3.53 (2H, s, H-7); 4.40 (2H, br. signal, NH_2), 6.40-7.20(4H, m, H-Ar).

Base (5). mp 65—66°C. IR (KBr): 3385, 3263, 3042, 2986, 2967, 2953, 2909, 2871, 2807, 2787, 2742, 2360, 1619, 1576, 1486, 1459, 1440, 1377, 1347, 1325, 1285, 1243, 1189, 1173, 1141, 1126, 1083, 1065, 986, 945, 886, 847, 753, 733, 713, 545.

Mass (*m/z*): 206(M^+), 189($M-NH_3$)$^+$, 177 (M-CHO), 160, 136 (M-70)$^+$, 84, 70.

PMR ($CDCl_3$, HMDS): 1.67 (4H, m, H-3′, H-4′); 2.04 (4H, m, H-2′, H-5′); 3.55 (2H, s, H-7); 3.78 (3H, s, OCH_3); 4.56 (2H, br. Signal, NH_2); 6.40-6.80 (3H, m, Har).

Base (6). mp 68—69°C. IR (KBr): 3448, 3289, 3041, 2967, 2928, 2903, 2870, 2809, 2730, 1609, 1409, 1457, 1439, 1419, 1371, 1348, 1321, 1290, 1203, 1154, 1138, 1118, 993, 948, 934, 908, 876, 814, 648, 625, 585, 536, 454.

Mass (*m/z*): 254/256(M^+), 237/239($M-NH_3$)$^+$, 225/227, 184/186(M-70)$^+$, 147, 105, 104, 84, 79/81, 76, 70.

PMR ($CDCl_3$, HMDS): 4.47 (4H, m, H-3′, H-4′); 2.38 (4H, m, H-2′, H-5′); 3.46 (2H, s, H-7); 4.47 (2H, br. signal, NH_2), 6.42, 7.14 (each 1H, d, J=8.0 Hz, H-6, H-5); 7.02 (1H, s, H-3).

Base (16). Obtained by the method of [6]. IR (KBr): 3250, 2933, 2884, 2835, 1644, 1614, 1581, 1503, 1482, 1455, 1428, 1387, 1283, 1254, 1234, 1115, 1076, 994, 953, 904, 846, 747, 666, 637, 532.

PMR ($CDCl_3$, HMDS): 2.03 (2H, H-10); 2.25 (2H, H-9); 3.65 (2H, H-11); 3.80 (3H, OCH_3), 4.88 (1H, NH); 4.95 (1H, H-2); 7.28 (1H, H-7); 7.45 (1H, H-6); 7.83 (1H, H-5).

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