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Synthesis, Mechanism of Formation and Spatial Arrangement of (2*S*,3*S*,6*R*)-2,6-Diphenyl-3,4-dimethyl-6-ol

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Abstract—Alkylation of alkaloid D-pseudoephedrine with bromoacetophenone results in a morpholine derivative. Structural and energy characteristics of the molecules of the starting, intermediate, and final reaction products were calculated by *ab initio* method in the HF/6-31G(d,p) approximation. The spatial structure of the final reaction product was determined by X-ray diffraction analysis.

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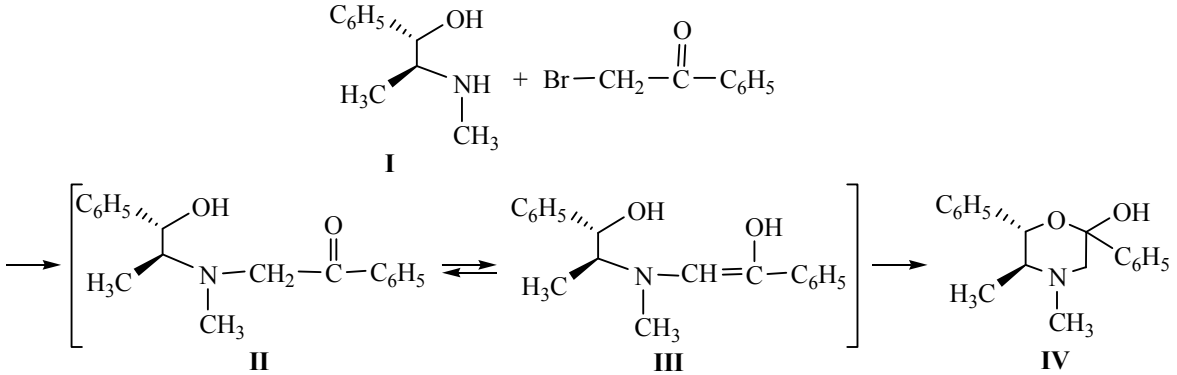
It is known that the introduction of the electron-deficient carbonyl group into the structure of ephedrine alkaloids often leads to intramolecular heterocycle closure [1]. For example, the reaction of L- ephedrine with chloroacetamide results in a cyclic compound morpholin-2-one [2]. However the alkylation of D- pseudo-ephedrine with chloroacetamide gives rise to the corresponding amide. It is known that L-ephedrine reacts with α-haloketone to form morpholine derivatives [3].

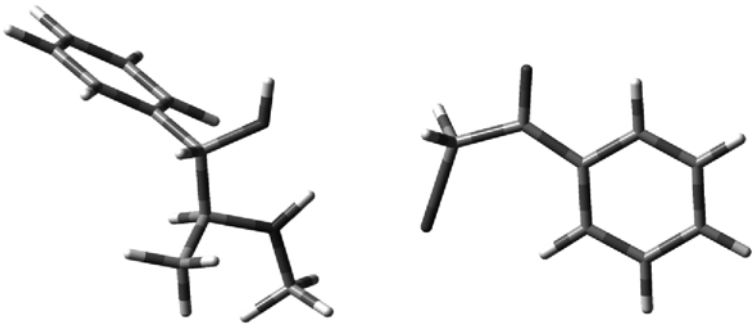
Continuing studies on the interaction of ephedrine alkaloids with compounds containing the reaction center in the α-position to the carbonyl group, we studied alkylation of D-pseudoephedrine **I** with phenacyl bromide in benzene in the presence of triethylamine.

The reaction affords the morpholine derivative, (2*S*,3*S*,6*R*)-biphenyl-3,4-dimethylmorpholin-6-ol **IV**, in a yield of 74%, instead of the expected amino ketone **II**.

The morpholine derivative is obtained probably via the intermediate formation of aminoketone, i.e., the first step is the alkylation of a secondary amino group of D-pseudoephedrine. Apparently, the resulting aminoketone may exist in a keto-enol form. Due to the presence of a reactive electron-deficient carbonyl group and a free hydroxy group of the alkaloid the intramolecular heterocyclization of enol form takes place to give a cyclic product, (2*S*,3*S*,6*R*)-biphenyl-3,4-dimethylmorpholin-6-ol **IV**.



I **II** **III** **IV**



E –516.7367 au *E* –2951.7813 au

Fig. 1. Spatial arrangement of the molecules of D-pseudoephedrine **I** and phenacyl bromide.

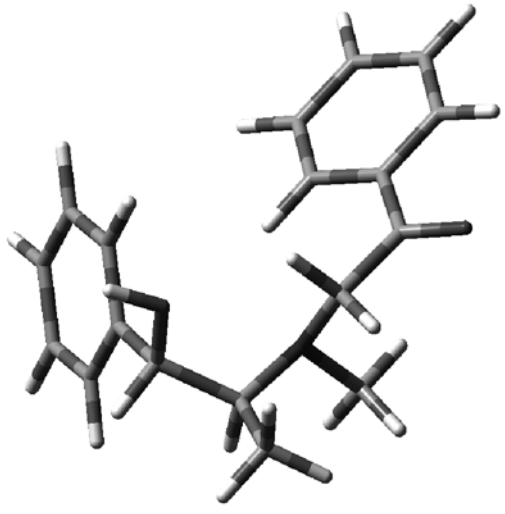
The proceeding of the intramolecular reactions requires the proximity and optimal orientation of the atoms of closing rings, i. e., the stereochemistry of the reactions depends on the structure of the starting compounds.

In order to analyze the causes of the instability of the intermediate aminoketone **II** we calculated the structure by *ab initio* quantum-chemical method HF/6-31G(d,p) [4] with the full optimization of geometry and energy characteristics of the molecules of the initial D-pseudoephedrine **I**, morpholine derivative **IV**, and intermediates **II**, **III**. Structures of the studied compounds are shown in Figs. 1–4. Also the values of their total energies are shown.

Starting compound **I** has a non-rigid conformation. In the molecule the internal rotation of the atomic groups around single bonds is possible. Figure 1 shows the conformation of molecule **I** most favorable by energy and the spatial structure of the phenacyl bromide molecule.

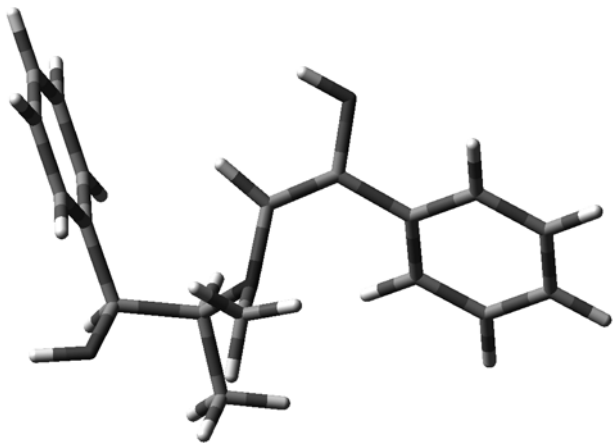
As suggested above, the aminoketone **II** can exist as keto-enol tautomers. According to the calculations data, the enol form **III** of aminoketone (Fig. 3) is destabilized compared to **II** by almost 70 kJ mol^{-1}, i. e., it is an unstable compound.

The intramolecular cyclization involving the carbon atom at the double bond occurs effectively if the molecular structure of one of the conformations is close to the spatial requirements of the transition state [5]. This requirement obviously is fulfilled in the case of intermediate **II**.



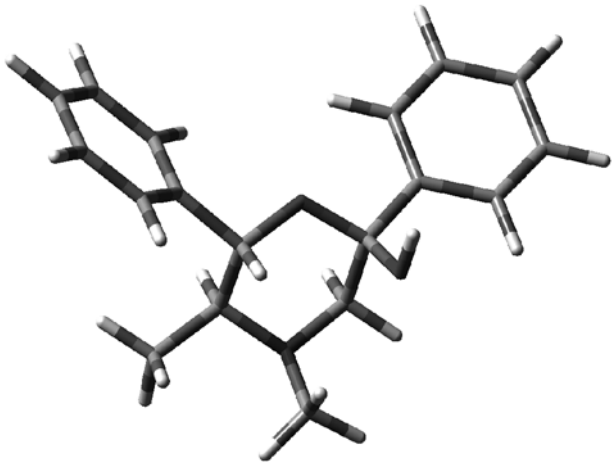
E –898.0474 au

Fig. 2. Spatial arrangement of the molecule of intermediate aminoketone **II**.



E –898.0205 au

Fig. 3. Spatial arrangement of the molecule of intermediate enol **III**.



E –898.0587 au

Fig. 4. Spatial arrangement of the molecule of **IV**.

Based on the foregoing, it may be concluded that α-aminoketone **II** cannot be a stable reaction product as its structure favors intramolecular nucleophilic interaction between the hydroxy and carbonyl groups leading to the formation only of a cyclic compound.

The IR spectrum of compound **IV** contains an absorption band of hydroxy groups in the range of 3420–3370 cm^{-1} and no absorption band of the carbonyl group. In order to determine the structure of compound **IV** we carried out its X-ray diffraction analysis. General view of the molecular structure of **IV** is shown in Fig. 5.

It was found that the unit cell contains three crystallographically independent molecules **IVa**–**IVc**. Bond lengths and bond angles in the molecular structure of **IVa**–**IVc** (Tables 1, 2) are close to normal [6].

In all three crystallographically independent structures the morpholine ring adopts a slightly distorted *chair* conformation: $\Delta C_S^1 = 2.3°$, $\Delta C_S^3 = 0.8°$ and $\Delta C_S^3 = 1.1°$ for molecules **IVa**–**IVc**, respectively (intracyclic torsion angles are given in Table 3).

Most of the morpholine derivatives exist in similar conformations [7]. More bulky substituents, phenyl and methyl group at the atom C^3, take the equatorial orientation; the hydroxy group is axially oriented.

The calculated and experimental structures of reaction product **IV** are identical except for the position of the hydroxyl hydrogen atom. Theoretical and experimental values of the geometric parameters are also close. For example, the torsion angle $O^{19}C^6C^{13}C^{14}$ –142.8° (calc.) and –148.8° (XRD), $O^1C^6C^{13}C^{14}$ –22.5° (calc.) and –27.1° (XRD), $C^6O^1C^2C^3$ –58.6° and –56.2°, etc.

Thus, it was shown that the major product of the reaction between alkaloid D-pseudoephedrine and phenacyl bromide is morpholine derivative, (2*S*,3*S*,6*R*)-biphenyl-3,4-dimethylmorpholin-6-ol, which may be formed by an intramolecular cyclization of an intermediate aminoketone.

EXPERIMENTAL

IR spectra were recorded on a Nicolet AVATAR-320 Fourier spectrometer from KBr pellets. Melting points were determined on a Boëtius instrument. TLC analysis was carried out on Sorbfil plates detecting with iodine vapor.

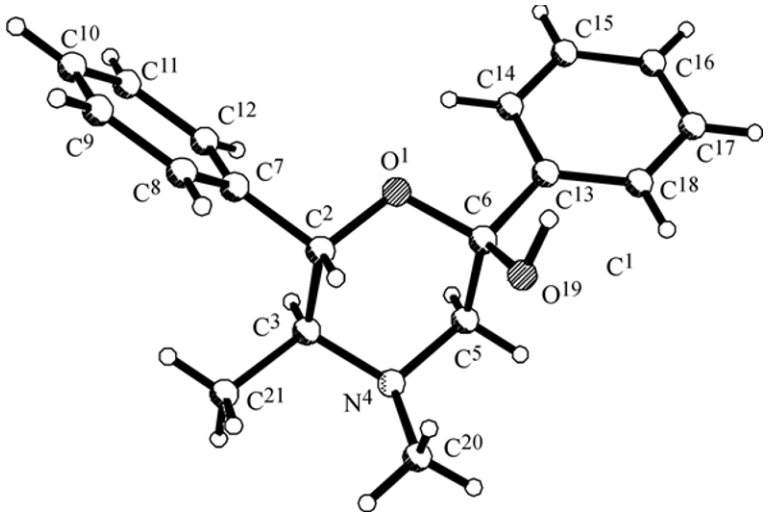


Fig. 5. General view of the molecule of (2*S*,3*S*,6*R*)-2,6-diphenyl-3,4-dimethylmorpholin-6-ol **IV**.

Table 1. Bonds lengths (*d*, Å) in the structure of **IV**

Bond	**IVa**	**IVb**	**IVc**	Bond	**IVa**	**IVb**	**IVc**
O^1–C^6	1.429(4)	1.428(5)	1.432(4)	C^7–C^{12}	1.367(7)	1.399(9)	1.385(5)
O^1–C^2	1.433(4)	1.435(5)	1.426(4)	C^8–C^9	1.372(8)	1.394(9)	1.381(6)
C^2–C^7	1.500(5)	1.531(5)	1.510(5)	C^9–C^{10}	1.352(9)	1.377(9)	1.372(6)
C^2–C^3	1.535(5)	1.503(6)	1.516(5)	C^{10}–C^{11}	1.372(9)	1.344(9)	1.367(7)
C^3–N^4	1.481(4)	1.488(5)	1.476(5)	C^{11}–C^{12}	1.383(7)	1.402(9)	1.379(6)
C^3–C^{21}	1.516(5)	1.511(6)	1.524(6)	C^{13}–C^{18}	1.373(6)	1.376(7)	1.388(5)
N^4–C^5	1.466(4)	1.464(5)	1.462(5)	C^{13}–C^{14}	1.394(6)	1.389(7)	1.393(5)
N^4–C^{20}	1.476(5)	1.479(5)	1.469(5)	C^{14}–C^{15}	1.379(6)	1.394(8)	1.366(6)
C^5–C^6	1.525(5)	1.524(5)	1.517(5)	C^{15}–C^{16}	1.362(9)	1.360(9)	1.369(7)
C^6–O^{19}	1.396(4)	1.401(4)	1.394(4)	C^{16}–C^{17}	1.380(8)	1.351(9)	1.368(6)
C^6–C^{13}	1.519(5)	1.505(6)	1.503(5)	C^{17}–C^{18}	1.395(6)	1.378(8)	1.385(6)
C^7–C^8	1.373(6)	1.383(8)	1.376(5)				

Table 2. Bond angles (ω, deg) in the structure of **IV**

Angle	**IVa**	**IVb**	**IVc**	Angle	**IVa**	**IVb**	**IVc**
$C^6O^1C^2$	113.9(3)	113.2(3)	113.4(3)	$C^8C^7C^{12}$	118.4(4)	119.3(6)	117.5(4)
$O^1C^2C^7$	106.2(3)	112.6(4)	105.2(3)	$C^8C^7C^2$	120.2(4)	120.9(6)	122.0(3)
$O^1C^2C^3$	110.6(3)	106.8(3)	111.8(3)	$C^{12}C^7C^2$	121.4(4)	119.7(6)	120.5(3)
$C^7C^2C^3$	112.9(3)	112.4(4)	114.0(3)	$C^7C^8C^9$	120.6(6)	120.6(9)	121.1(4)
$N^4C^3C^2$	111.9(3)	109.7(3)	110.6(3)	$C^{10}C^9C^8$	120.9(6)	118.3(9)	120.1(4)
$N^4C^3C^{21}$	112.4(3)	111.1(3)	109.9(3)	$C^9C^{10}C^{11}$	119.5(6)	122.7(9)	119.6(4)
$C^2C^3C^{21}$	111.2(3)	109.6(4)	110.1(4)	$C^{10}C^{11}C^{12}$	119.6(6)	119.4(9)	119.9(5)
$C^5N^4C^{20}$	112.7(3)	107.7(3)	110.3(3)	$C^7C^{12}C^{11}$	121.0(5)	119.5(9)	121.7(4)
$C^5N^4C^3$	109.7(2)	110.0(3)	109.0(3)	$C^{18}C^{13}C^{14}$	118.6(4)	118.3(5)	117.2(4)
$C^{20}N^4C^3$	115.5(3)	111.4(3)	111.9(3)	$C^{18}C^{13}C^6$	120.3(4)	123.3(5)	121.5(3)
$N^4C^5C^6$	116.1(3)	113.2(3)	111.7(3)	$C^{14}C^{13}C^6$	121.0(4)	118.4(4)	121.3(3)
$O^{19}C^6O^1$	110.8(3)	110.8(3)	111.1(3)	$C^{15}C^{14}C^{13}$	120.5(5)	119.5(6)	121.3(4)
$O^{19}C^6C^{13}$	112.6(3)	111.3(3)	112.1(3)	$C^{16}C^{15}C^{14}$	120.6(5)	121.3(7)	121.1(4)
$O^1C^6C^{13}$	106.7(3)	107.5(3)	105.9(3)	$C^{15}C^{16}C^{17}$	119.8(5)	119.4(7)	118.9(4)
$O^{19}C^6C^5$	108.7(3)	108.3(3)	108.3(3)	$C^{16}C^{17}C^{18}$	119.8(5)	120.7(8)	120.6(4)
$O^1C^6C^5$	108.8(3)	108.9(3)	108.1(3)	$C^{13}C^{18}C^{17}$	120.6(5)	120.7(7)	120.9(4)
$C^{13}C^6C^5$	109.2(3)	110.0(3)	111.3(3)				

Table 3. Torsion angles (τ, deg) in the structure of morpholine moiety in **IV**

Angle	**IVa**	**IVb**	**IVc**	Angle	**IVa**	**IVb**	**IVc**
$C^6O^1C^2C^3$	–58.4(4)	–56.6(4)	–57.2(4)	$C^3N^4C^5C^6$	50.3(4)	56.1(4)	57.6(4)
$O^1C^2C^3N^4$	54.7(4)	53.8(4)	53.8(4)	$N^4C^5C^6O^1$	–52.1(4)	–56.5(4)	–57.8(4)
$C^2C^3N^4C^5$	–50.1(4)	–53.0(4)	–54.2(4)	$C^2O^1C^6C^5$	55.4(3)	55.9(3)	57.5(4)

XRD analysis of compound IV. Unit cell parameters and intensities of 5346 independent reflections were measured at 23°C on a Bruker P4 automatic four-circle diffractometer (graphite monochromator, MoK_α-radiation, θ/2θ-scanning, 2θ ≤ 52°). The crystals are orthorhombic; unit cell parameters: *a* 12.4477(12), *b* 13.6756(15), *c* 29.188(3), *V* 4968.6(8) Å^3, d_{calc} 1.136 g cm^{-3}, *Z* 12 ($C_{216}H_{252}N_{12}O_{24}$), space group $P2_12_12_1$.

In the calculations 4151 reflections with intensity of $I \geq 2\sigma$ were used. The structure was solved by the direct method and refined by full-matrix anisotropic approximation for non-hydrogen atoms. Except for H atoms of hydroxy groups identified from the difference synthesis and refined isotropically, the hydrogen atoms were placed geometrically and refined in a *rider* model The correction for extinction was performed using ψ-curves. The final divergence factors are *R* 0.0493, wR_2 0.1203. The structure was solved and refined by the programs SHELXS-97 [8] and SHELXL-97 [9]. The atomic coordinates were deposited at the Cambridge Crystallographic Data Centre (CCDC 915055).

(2*S*,3*S*,6*R*)-Biphenyl-3,4-dimethylmorpholin-6-ol (IV). To a solution of 2 g (0.012 mol) of D-pseudoephedrine **I** in 10 mL of benzene were added 1.22 g (0.012 mol) of triethylamine and 2.39 g (0.012 mol) of bromoacetophenone dissolved in 7 mL of benzene. The reaction mixture was stirred at 50–60°C for 4 h. Then precipitated triethylamine hydrobromide was filtered off, and the solvent was removed. The residue was chromatographed on silica gel eluting with benzene. Yield 2.54 g (74 %), mp 84–85°C.

REFERENCES

1. Nurkenov, O.A., Gazaliev, A.M., and Kanakhin, A.V., *Zh. Obshch. Khim.*, 2000, vol. 70, no. 12, p. 2059.
2. Dieter, R.K., Lagu, B., Dieter, J.W., Deo, N., and Pennington, W.T., *Synlett.*, 1990, no. 2, p. 109.
3. Baramysova, G.T., *Cadidate Dissert. (Chem.)*, Almaty, 1999.
4. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, J.A., Jr., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C., and Pople, J.A., *GAUSSIAN 03*, Revision A.1, Gaussian Inc., Pittsburgh PA, 2003.
5. Minkin, V.I., Simkin, B.Ya., and Minyaev, R.M., *Kvantovaya khimiya organicheskikh soedinenii* (Quantum Chemistry of Organic Compounds), Moscow: Khimiya, 1986.
6. Allen, F.H., Kennard, O., Watson, D.G., Bramer, L., Orpon, A.G., and Taylor, R., *J. Chem. Soc., Perkin Trans. 2*, 1987, no. 3, p. 1356.
7. *Cambridge Crystallographic Database*, Release 2011, Cambridge.
8. Sheldrick, G.M., *Acta Crystaollogr. (A)*, 2008, vol. 64, p. 112.
9. Sheldrick, G.M., *SHELXL97. Program for the Refinement of Crystal Structure*, Göttingen University, Göttingen, Germany, 1997.