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Reaction of *d*-Pseudoephedrine Hydrochloride with Anisaldehyde in the Presence of Sodium Cyanide

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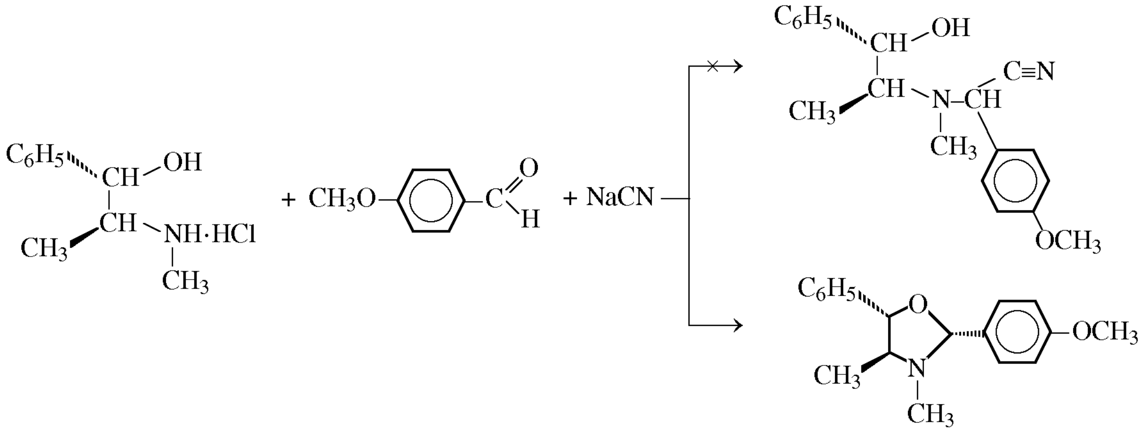
Abstract—2-(*p*-Methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3-oxadiazolidine was synthesized, and its steric structure was studied by X-ray diffraction.

As reported earlier [1], ephedrine alkaloids (*l*-ephedrine and *d*-pseudoephedrine) react with symmetrical cyanhydrines to give corresponding nitriles. The reaction of *l*-ephedrine with aromatic aldehydes in the presence of sodium cyanide gives rise to α-aminonitriles [2, 3]. However, reacting *d*-pseudoephedrine with anisaldehyde in similar conditions we found that the synthesis leads to a heterocyclic compound, 2-(*p*-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3-oxazolidine (**I**), rather that the expected α-aminonitrile. Apparently, this results is explained by the fact that *d*-pseudoephedrine hydrochloride in the presence of sodium cyanide transforms into a base which condenses with the aldehyde to give the heterocyclic compound.



I

The steric structure of compound **I** was established by X-ray diffraction. The resulting structure is shown in the figure. The bond lengths and bond angles are close to normal [4]. The oxazolidine ring in **I** takes a slightly distorted 3-*evelope* conformation (ΔC_s^3 8.4°) (the endocyclic torsion angles $O^1C^2N^3C^4$, $C^2N^3C^4C^5$, $N^3C^4C^5O^1$, $C^4C^5O^1C^2$, and $C^5O^1C^2N^3$ are 42.0, –46.6, 33.2, –7.5, and –21.5°, respectively). The N^3 atom deviates from the plane defined by the other ring atoms by 0.667 Å, and the O^1, C^2, C^4, and C^5 atoms are coplanar within ±0.033 Å. In the 3-*envelope* conformation, the methyl groups on N^3 and C^4 and the methoxyphenyl group are equatorial (the torsion angles $C^{13}N^3C^4C^5$, $C^{14}C^4N^3C^2$, and $C^6C^2N^3C^4$ are –167.6, –168.6, and 162.0°, respectively), while the phenyl group is pseudoequatorial (the torsion angle

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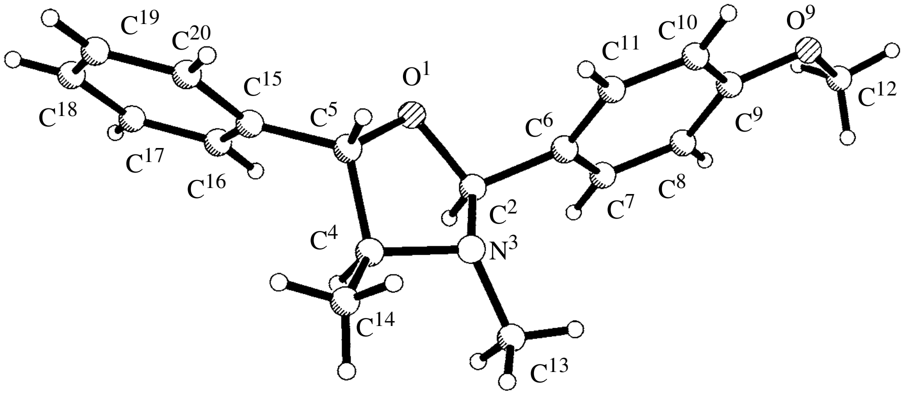

Molecular structure of compound **I**.

$C^{15}C^5C^4N^3$ is 154.9°). The 3-*envelope* conformation is also characteristic of (2*S*,4*S*,5*S*)-3,4-dimethyl-5-phenyl-2-(phenylethynyl)-1,3-oxazolidine [5].

Since the *l*-ephedrine and *d*-pseudoephedrine derivatives bear substituents on N^3, C^4, and C^5, one more favorable conformation of the ring is 4-*envelope*, where the methyl group on C^4 is equatorial, and the substituents on the other two mentioned atoms are pseudoequatorial. The 4-*envelope* conformation is most common in pseudoephedrine oxazolidine derivatives, specifically, 2-(methoxycarbonyl)-3,4-dimethyl-5-phenyl-1,3-oxazolidine [6].

EXPERIMENTAL

The IR spectrum was measured on a UR-20 instrument (KBr). The ^{1}H NMR spectrum was obtained on a Tesla BS-587 spectrometer (80 MHz) in C_6D_6 relative to internal HMDS. The melting point was measured on a Boëtuis hot stage.

X-ray diffraction experiment. The unit cell parameters and the intensities of 1702 unique reflections of crystal **I** were measured at 20°C on a Bruker-P4 automatic four-circle diffractometer with monochromatic λMoK_α radiation (∞/2∞ scanning, 2∞ ≤ 60°). Orthorhombic crystals, *a* 6.156(1), *b* 14.211(3), *c*

Atomic coordinates (× 10^4; for H atoms, × 10^3) in molecule **I**

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
O^1	2542(4)	3378(2)	1401(2)	H^3	561(7)	291(3)	37(3)
O^2	5263(6)	1480(3)	5313(2)	H^4	684(6)	115(3)	14(2)
N^1	2325(4)	1668(2)	1656(2)	H^5	515(7)	–23(3)	80(2)
C^2	3259(6)	2516(2)	1256(2)	H^7	209(6)	–78(3)	164(2)
C^3	4997(7)	2296(3)	700(2)	H^{8a}	–108(6)	–56(3)	246(2)
C^4	5644(7)	1335(3)	556(2)	H^{8b}	–109(6)	28(3)	155(2)
C^5	4648(6)	510(3)	969(2)	H^9	–209(6)	119(3)	291(2)
C^6	3012(5)	690(2)	1517(2)	H^{10a}	–62(6)	220(3)	183(2)
C^7	1944(6)	–170(2)	1995(2)	H^{10b}	94(6)	250(3)	258(2)
C^8	–394(6)	65(3)	2148(3)	H^{11a}	71(6)	146(3)	392(2)
C^9	–435(5)	1020(3)	2700(2)	H^{11b}	–12(5)	31(2)	388(2)
C^{10}	472(6)	1928(3)	2207(3)	H^{13a}	463(5)	–51(2)	276(2)
C^{11}	742(6)	831(3)	3540(2)	H^{13b}	234(5)	–98(2)	312(2)
N^{12}	2962(4)	562(2)	3374(2)	H^{14a}	353(6)	2(2)	458(2)
C^{13}	3069(6)	–359(2)	2847(2)	H^{14b}	565(6)	–1(2)	409(2)
C^{14}	4196(7)	452(3)	4157(2)	H^{16a}	499(8)	228(3)	347(3)
C^{15}	4852(7)	1448(3)	4558(2)	H^{16b}	599(8)	280(3)	417(3)
C^{16}	5029(10)	2385(3)	4017(3)	H^{16c}	359(6)	282(5)	402(4)

18.878(1) Å; V 1651.5(2) Å^3, d_{calc} 1.14 g/cm^3, Z 4, $C_{18}H_{21}NO_2$, space group $P2_12_12_1$.

In calculations we used 942 reflections with $I \geq 2\sigma(I)$. The structure was solved by the direct method and refined by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were fixed geometrically and were not refined. Weight parameter 0.1725. The structure was refined to R 0.0705 and R_W 0.2332. All calculations were performed on an RS/AT-200 computer using the SHELXL 97 program package. The coordinates of non-hydrogen atoms are given in the table.

(2*S*,4*S*,5*S*)-2-(*p*-Methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3-oxazolidine (I). To a mixture of 2.8 g of *d*-pseudoephedrine hydrochloride in 5 ml of acetonitrile we added with stirring at room temperature 3.59 g of *p*-methoxybenzaldehyde and then, slowly, a solution of 0.68 g of sodium cyanide in 2 ml of water. The mixture was stirred at room temperature for 5 h. The reaction products were extracted with ethyl acetate, the extracts were dried with $MgSO_4$, the solvent was removed by distillation, and the residue was passed through a silica gel column, eluent ethyl acetate–hexane (15:85). Yield 1.68 g (42.8%), mp 62–63°C. ^{1}H NMR spectrum, δ, ppm: 1.15 d (3H, CH_3CH, J_{HH} 5.8 Hz), 2.15 s (3H, CH_3N), 2.52 m (1H, CHN), 3.82 s (3H, CH_3O), 5.10 s (1H, NCHO), 4.80 d (1H, CHO, J_{HH} 6.6 Hz), 7.51 m (5H, C_6H_5). Found, %: C 76.01; H 7.38; N 4.91. $C_{18}H_{21}NO_2$. Calculated, %: C 76.32; H 7.42; N 4.95.

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