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Reaction of Chloroacetone with Cytisine and *d*-Pseudoephedrine Alkaloids

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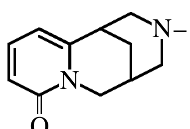
Abstract—Alkylation of cytisine and *d*-pseudoephedrine alkaloids with chloroacetone was performed. The target product of the reaction with cytisine is aminoacetone and of the reaction with *d*-pseudoephedrine, a morpholine derivative.

It is known from published data [1] that α-aminoketones and their derivatives play an important role in many biological processes, and their synthesis from natural compounds presents great interest for designing new pharmacologically active compounds. It is the α position of the amino and carbonyl groups which is responsible for the diverse biological activity of such compounds, since it favors stronger interactions of biologically active compounds with the surface of the substrates.

Extending the search for biologically active compounds we have synthesized aminoketones on the basis of cytisine and *d*-pseudoephedrine alkaloids **I** and **II**. The alkaloids were reacted with chloroacetone in benzene in the presence of triethylamine.

$$\underset{\textbf{I, II}}{RH} + ClCH_2C(O)CH_3 \xrightarrow{(C_2H_5)_3N} \underset{\textbf{III, IV}}{RCH_2C(O)CH_3},$$

R =  (**I, III**),

C_6H_5–CH(OH)–CH(CH$_3$)–N(CH$_3$)– (**II, IV**).

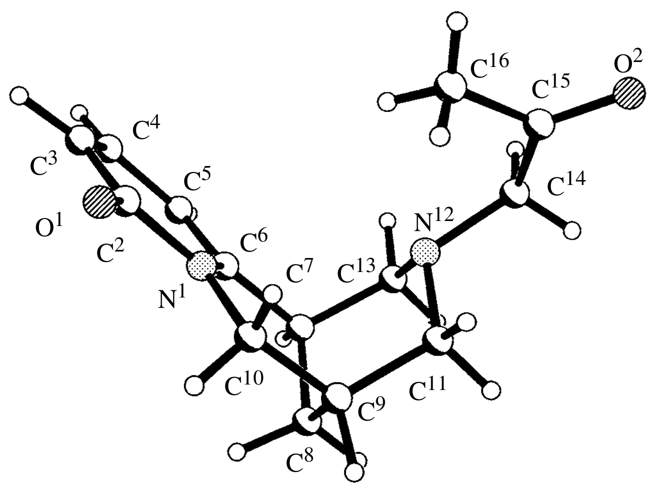
N-Acetonylcytisine (**III**) is a crystalline compound. Its IR spectrum shows a characteristic carbonyl absorption band near 1712 cm^{-1}, and the ^{1}H NMR spectrum shows cytisine and acetonyl proton signals.

The steric structure of *N*-acetonylcytisine (**III**) was established by X-ray diffraction (see figure). It was found that the bond lengths (Table 1) and bond angles in the cytisine carcass are close to respective values in

Table 1. Bond lengths (*d*, Å) in compound **III**

Bond	*d*	Bond	*d*
O^1–C^2	1.242(4)	C^7–C^8	1.524(5)
O^2–C^{15}	1.211(5)	C^7–C^{13}	1.531(5)
N^1–C^2	1.410(4)	C^8–C^9	1.526(5)
N^1–C^6	1.376(4)	C^9–C^{10}	1.534(5)
N^1–C^{10}	1.491(5)	C^9–C^{11}	1.530(5)
C^2–C^3	1.428(5)	C^{11}–N^{12}	1.467(5)
C^3–C^4	1.349(6)	N^{12}–C^{13}	1.469(4)
C^4–C^5	1.411(5)	N^{12}–C^{14}	1.458(5)
C^5–C^6	1.361(5)	C^{14}–C^{15}	1.511(5)
C^6–C^7	1.515(4)	C^{15}–C^{16}	1.500(6)

(–)-cytisine (**I**) [2, 3], (–)-*N*-methylcytisine (**V**) [3], and *N*-(dimethoxyphosphoryl)cytisine (**VI**) [4], except that the C^2–O^1 bond [1.243(3) Å] is longer than standard (1.222 Å in benzodienones [5]). The confi-



Molecular structure of compound **III**.

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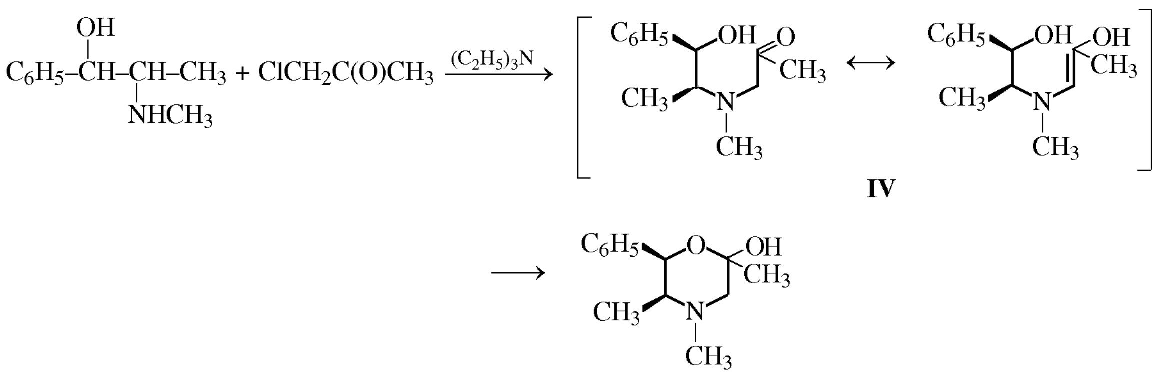
guration of N^{12} in *N*-acetonylcytisine (**III**) in pyramidal, like in **V** (the sums of bond angles are 334.2 and 331.9°, respectively), whereas in **VI** it is almost planar-trigonal (354.8°) as a result of the steric strain produced by the bulky dimethoxyphosphoryl substituent.

The conformation of the cytisine carcass in *N*-acetonylcytisine is the same as in **I** and **VI**. The dihydropyridine ring is planar to within ±0.005 Å, and the carbonyl O^1 atom practically resides in this plane, deviating by as little as 0.029 Å. The conformation of the tetrahydropyridine ring is slightly distorted *sofa* (ΔC_s^8 4.5°), and the bridging C^8 atom deviates from the mean plane defined by the other ring atoms (accurate to within ±0.02 Å) is 0.75 Å. The piperidine ring has an almost ideal *chair* conformation (ΔC_s^8 1.0°), the C^8 and N^{12} atoms deviating from the mean plane defined by the other atoms (±0.006 Å) by 0.744 and 0.681 Å, respectively, in opposite directions. The acetonyl group on N^{12} is equatorial relative to the piperidine ring (the $C^7C^{13}N^{12}C^{14}$ and $C^9C^{11}N^{12}C^{14}$ torsion angles are 174.5° and 175.3°, respectively).

Examining the ^{1}H NMR and IR spectra of *N*-acetonyl-*d*-pseudoephedrine (**IV**) (colorless distillable oil) we came to a conclusion that the resulting product is a cyclic morpholine derivative of *d*-pseudoephedrine (compound **VII**).

It is known that ephedrine alkaloids, being polyfunctional compounds, have two reaction centers and are prone to cyclization yielding morpholines and oxazolidines [6, 7]. The first stage involves alkylation of *d*-pseudoephedrine by the amino group and formation of intermediate *N*-acetonyl-*d*-pseudoephedrine (**IV**). Due to the presence of a reactive electron-deficient carbonyl group and a free hydroxy group, the enolic form of the latter undergoes intramolecular heterocyclization to give a cyclic alcohol, (5*S*,6*S*)-2,4,5-trimethyl-6-phenylperhydro-1,4-oxazin-2-ol (**VII**).

The IR spectrum of compound **VII** contains aryl C=C and hydroxyl bands at 1685 and 3430–3380 cm^{-1}, respectively, and no carbonyl band.



IV

VIII

The ^{1}H NMR spectrum of compound **VII**, the CH_3C proton signal appear near 0.63 ppm as a doublet with a coupling constant of 6.8 Hz. The $CH_3C(O)$ methyl gives a singlet at 1.72 ppm, and the *N*-methyl singlet is near 2.15 ppm. The CHN proton appears as a complex multiplet at 2.43–2.65 ppm, and the doublet at 50 ppm belongs to the CHO proton (J_{HH} 7.3 Hz). The singlet near 2.53 ppm is assignable to the NCH_2 protons. The signals of benzene ring protons are observed near 7.08 ppm.

EXPERIMENTAL

The IR spectra were measured on a UR-20 instrument (KBr). The ^{1}H NMR spectra were recorded on a Tesla BS-597 spectrometer (80 MHZ) for C_6D_6 solutions, external reference HMDS. The melting point was determined on a Boetuis hot stage.

X-ray diffraction experiment. The unit cell parameters and the intensities of 2175 reflections were measured on a Siemens R3/PC automatic four-circle diffractometer (λMoK_α radiation, graphite monochromator, θ/2θ scanning, 2θ < 60°). Rhombic crystals, *a* 6.302(1), *b* 13.166(3), *c* 15.652(3) Å; *V* 1298.7 $Å^3$, *M* 246.3, d_{calc} 1.259 g/cm^3, *Z* 4, $C_{14}H_{18}N_2O_2$. Space group $P2_12_12_1$.

In calculations we used 1380 unique reflections with $I \geq 3\sigma$. The structure was solved by the direct method and refined by full-matrix least-squares anisotropically for non-hydrogen atoms and isotropically

Table 2. Atomic coordinates ($\times 10^4$, for atoms H $\times 10^3$) in compound **III**

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

for hydrogens (all H atoms were revealed by difference synthesis) to R 0.037 and R_W 0.034. All calculations were performed using the Siemens SHELXTL 97 program package (PC Version). The atomic coordinates are given in Table 2.

***N*-Acetonylcytisine (III)**. To a solution of 5.13 g of cytisine and 2.73 g of triethylamine in 150 ml of dry benzene, 3.73 g of chloroacetone was added dropwise with stirring at 45–50°C, and the reaction mixture was stirred at the same temperature for 5 h. The precipitate of triethylamine hydrochloride was filtered off, the solvent was removed in a vacuum, and the residue was recrystallized from hexane to obtain 4.65 g (70%) of compound **III**, mp 113–114°C.

(5*S*,6*S*)-2,4,5-Trimethyl-6-phenylperhydro-1,4-oxazin-2-ol (VII). To a refluxed solution of 4.95 g of *d*-pseudoephedrine and 4.54 g triethylamine in 40 ml of dry benzene, 2.7 g of chloroacetone in 10 ml of benzene was added dropwise with stirring. The mixture was boiled for 3 h. The precipitate of triethylamine hydrochloride was filtered off, the solvent was removed in a vacuum, and the residue was subjected to column chromatography on Al_2O_3, eluent benzene. Vacuum distillation [bp 126°C (2 mm)] gave 57% of compound **VII**.

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