Russian Journal of Organic Chemistry, Vol. 38, No. 5, 2002, pp. 662–664. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 5, 2002, pp. 699–702.

Mannich Condensation of *exo*-2,*exo*-6-Tricyclo[5.2.1.$0^{2,6}$]decan-8-one

S. S. Koval'skaya and N. G. Kozlov

Institute of Physical Organic Chemistry, Belarussian National Academy of Sciences, ul. Surganova 13, Minsk, 220072 Belarus

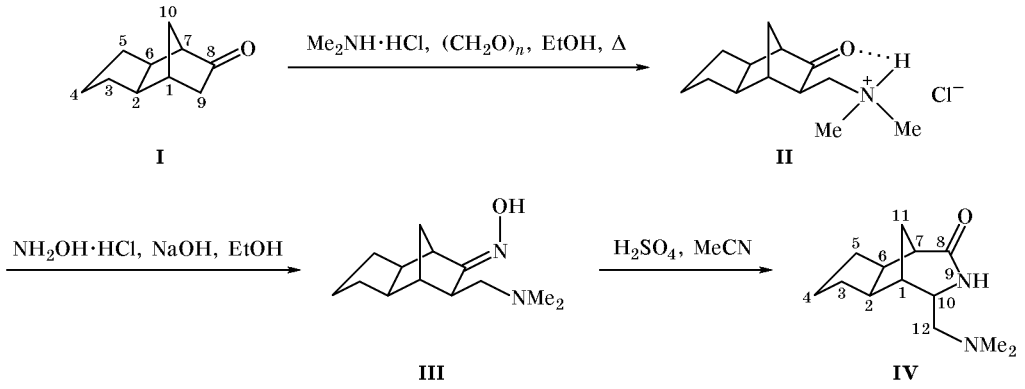
Received April 6, 2001

Abstract—Mannich condensation of *exo*-2,*exo*-6-tricyclo[5.2.1.$0^{2,6}$]decan-8-one with paraformaldehyde and dimethylamine hydrochloride results in the addition of dimethylaminomethyl fragment at the C^9 atom to give the *exo*-9-isomer. The reaction of *exo*-9-dimethylaminomethyl-*exo*-2,*exo*-6-tricyclo[5.2.1.$0^{2,6}$]decan-8-one with hydroxylamine hydrochloride in alcoholic alkali yields the corresponding *Z*-oxime which undergoes selective rearrangement into *exo*-10-dimethylaminomethyl-9-aza-*exo*-2,*exo*-6-tricyclo[5.3.1.$0^{2,6}$]undecan-8-one by the action of sulfuric acid in acetonitrile.

The interest in selective transformations leading to nitrogen-containing bridged polycyclic systems is stimulated mainly by the fact that a large number of biologically active compounds have been found among such products [1–3]. Mannich condensation is one of the methods allowing introduction of an amino group into polycyclic ketone molecules. This reaction is advantageous due to its high regio- and stereoselectivity. Moreover, the resulting aminoketones are highly reactive compounds which can be brought into further transformations with the goal of obtaining versatile products.

We previously demonstrated the possibility for transformation of bicyclic Mannich bases into aminolactams [4, 5], β-diamides [6], tricyclic pyridine derivatives [7], and also carbocyclic prostaglandin analogs and their precursors [7, 8]. We now report on the Mannich condensation of *exo*-2,*exo*-6-tricyclo-[5.2.1.$0^{2,6}$]decan-8-one (**I**) with paraformaldehyde and dimethylamine hydrochloride under the conditions described by us previously for isocamphanone [4]. The reaction follows the same pattern: dimethylaminomethyl fragment adds not at the most substituted methine carbon atom (as in the case of most alicyclic ketones [9, 10]), but at the α-methylene group, namely at the C^9 atom (Scheme 1). The addition occurs from the spatially more accessible *exo* side. The rate of the reaction is much lower than with other alicyclic ketones. Like with isocamphanone, this is the result of thermodynamically unfavorable enolization of ketones having a strained bi- or tricyclic skeleton (such enolization gives rise to even stronger increase of angular strain). The structure of the product, *exo*-9-dimethylaminomethyl-*exo*-2,*exo*-6-tri-

Scheme 1.



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

1070-4280/02/3805-0662 $27.00 © 2002 MAIK "Nauka / Interperiodica"

cyclo[5.2.1.0^{2,6}]decan-8-one hydrochloride (**II**), was established on the basis of the IR and ^{1}H NMR spectra. Aminoketone **II** shows in the IR spectrum a band at 3450 cm^{-1}, which is typical of stretching vibrations of amino group, bands at 2790, 2750, and 2450 cm^{-1}, belonging to $\overset{+}{\text{N}}-\text{H}$ vibrations, and a band at 1745 cm^{-1} due to stretching vibrations of the carbonyl group. The ^{1}H NMR spectrum of **II** contained signals at δ 2.97 ppm (6H) from methyl protons at the nitrogen atom and δ 3.26 ppm (br.s) from one of the NCH_2 protons. Obviously, the signal from the other proton of this group is overlapped by the solvent signal (CD_3OD, δ 3.34 ppm). The 9-H signal appears as a broadened singlet at δ 2.92 ppm. In keeping with our previous data [4], the lack of a clearly defined spin–spin coupling between 9-H and 11-H indicates restricted rotation about the C^9-C^{11} bond. Otherwise, the corresponding vicinal constant would be observed (~7 Hz). The aminomethyl fragment in **II**, as well as in the other Mannich bases described by us previously, has no conformational freedom because of formation of a strong intramolecular hydrogen bond between the NH group and carbonyl oxygen atom. This hydrogen bond fixes the only conformation where the dihedral angles between the bonds formed by the 9-H and two 11-H atoms are close to 90°; the result is that the corresponding coupling constants are very small (<2 Hz).

Furthermore, the 9-H signal appears as a broadened singlet, indicating *endo* orientation of 9-H. Had the 9-H proton been oriented *exo*, its vicinal coupling constant with 1-H would be ~4–5 Hz, and the signals would be doublets. Thus we believe it unambiguously proved that the dimethylaminomethyl group on C^9 in molecule **II** is oriented *exo*. In the ^{1}H NMR spectrum of **II** we also identified signals from protons in the bridgehead positions, δ 2.40 and 2.43 ppm (1-H, 7-H, br.s) and δ 1.80 and 1.86 ppm (2-H, 6-H, br.s).

Treatment of aminoketone **II** with hydroxylamine hydrochloride resulted in selective formation of *Z*-oxime **III**. Its structure was established on the basis of the IR and ^{1}H NMR spectra. The IR spectrum of **III** contains no carbonyl band typical of ketone **II**, but a weak band at 1670 cm^{-1} is observed, which corresponds to stretching vibrations of the C=N bond. Also, absorption bands at 950 (N–O) and 3450 cm^{-1} (NO–H) were present. The ^{1}H NMR spectrum of **III** contained the following signals, δ, ppm: 2.33 s (6H, NMe), 2.55 m (2H, NCH_2), 2.43 t (9-H, ^3J = 6.8 Hz). The multiplicities of the 9-H and NCH_2 signals of **III** are different from those observed in the spectrum of **II**, indicating that the aminomethyl substituent in the former has a conformational freedom: There is no possibility for inramolecular H-bonding between the amino nitrogen atom and *Z*-hydroxyimino group. The *Z* orientation of the hydroxyimino group in **III** also follows from a considerable downfield shift of the 7-H signal (δ 3.07 ppm, br.s) relative to both the corresponding signal of **II** and the 9-H signal. It is known that such a downfield shift is typical of protons which are spatially close to hydroxyimino group [11]. Signals from the other bridgehead protons (which also appear as broadened singlets) are displaced insignificantly (see Experimental). Selective formation of *Z* isomers of amino oximes was also observed for Mannich bases derived from isocamphanone [4] and verbanone [5].

We showed in [11] that under conditions of the Ritter reaction the hydroxyimino group in strained bicyclic oximes smoothly rearranges into lactam provided that it is not shielded by methyl substituents. According to our previous data [4], the presence of aminomethyl group does not affect the rearrangement. Treatment of oxime **III** with sulfuric acid in acetonitrile gave the corresponding aminolactam, *exo*-10-dimethylaminomethyl-9-azatricyclo[5.3.1.0^{2,6}]undecan-8-one (**IV**), in contrast to aminooximes with a pinane skeleton, which undergo partial deamination under analogous conditions [5]. The structure of aminolactam **IV** was proved by IR and ^{1}H NMR spectroscopy. In the IR spectrum of **IV** we observed a band at 1660 cm^{-1}, typical of lactam carbonyl. The most downfield signal in the ^{1}H NMR spectrum of **IV** is that from the 10-H proton, δ 3.67 ppm, m, $^3J_{10,12}$ = 6.6, $^3J_{10,NH}$ = 8.0, $^3J_{10,1}$ = 2.4 Hz. The positions and multiplicities of signals from the methyl and methylene groups attached to nitrogen are almost the same as in the spectrum of initial aminooxime **III** (see Experimental). The positions of the 1-H, 2-H, and 6-H signals also change only slightly. The 7-H signal appears in a stronger field, δ 2.22 ppm (br.s), relative to the corresponding signal of oxime **III**. If the hydroxyimino group in **III** had *E* configuration, 8-azalactam would be formed for which the 7-H signal would be the most downfield (δ ~3.2 ppm).

Thus the transformations of tricyclic ketone **I** follow the same chemical and steric general relations as those observed previously for its bicyclic analog, isocamphanone [4].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS-567 spectrometer operating at 100 MHz. The IR spectra were measured on a UR-20 instrument. The progress of reactions and the purity of products were

monitored by GLC on a Chrom-5 chromatograph; 2000 × 2-mm glass column packed with Apiezon L on Chromaton N-AW-DMCS (160–200 μm).

***exo*-9-Dimethylaminomethyl-*exo*-2,*exo*-6-tricyclo[5.2.1.0^{2,6}]decan-8-one (II).** *exo*-2,*exo*-6-Tricyclo[5.2.1.0^{2,6}]decan-8-one, 2.3 g (15 mmol), was dissolved in 10 ml of ethanol, and 0.69 g (23 mmol) of paraformaldehyde and 1.63 g (20 mmol) of dimethylamine hydrochloride were added. The mixture was refluxed until the reaction was complete (~25 h, GLC monitoring). Evaporation of the solution gave 3.2 g (86%) of aminoketone hydrochloride **II** containing a small amount of unreacted dimethylamine hydrochloride. The resulting Mannich base was purified by recrystallization from chloroform where the product is satisfactorily soluble on heating while the impurity is almost insoluble. The chloroform solution was filtered while hot and was left to stand for crystallization. Aminoketone **II** purified in such a way had mp 206–208°C. Yield 3.08 g (83%). IR spectrum, ν, cm^{-1}: 3450 (NH); 2970, 2875, 2850 (CH); 2790, 2750, 2450 ($\overset{+}{N}$H); 1745 (C=O). ^{1}H NMR spectrum (CD_3OD), δ, ppm: ~3.33 br.s (1H, 11-H, the signal is overlapped by the multiplet solvent signal), 3.26 br.s (1H, 11-H), 2.97 s [6H, $N(CH_3)_2$], 2.92 br.s (1H, 9-H), 2.43 br.s (1H, 7-H), 2.40 br.s (1H, 1-H), 2.36–1.94 m (4H), 1.86 br.s and 1.80 br.s (1H each, 2-H and 6-H), 1.61–1.04 m (4H).

(*Z*)-*exo*-9-Dimethylaminomethyl-*exo*-2,*exo*-6-tricyclo[5.2.1.0^{2,6}]decan-8-one oxime (III). Potassium hydroxide, 0.52 g (9.2 mmol), was added to a solution of 0.4 g (5.7 mmol) of hydroxylamine hydrochloride in 10 ml of ethanol, and the mixture was stirred until the alkali dissolved completely. The precipitate of KCl was filtered off, 0.86 g (3.5 mmol) of aminoketone hydrochloride was added to the resulting alkaline solution of hydroxylamine, and the mixture was stirred at room temperature until the reaction was complete (about 3 days, GLC monitoring). The mixture was diluted with a 10-fold amount of water and extracted with chloroform (oxime **III** is very poorly soluble in ether), and the extract was dried over Na_2SO_4. The solvent was distilled off on a rotary evaporator, and the residue was recrystallized from alcohol. Yield 0.64 g (82%). mp 137–139°C. IR spectrum, ν, cm^{-1}: 3450 (NOH); 2970, 2930, 2820 (C–H); 1670 w (C=N); 950 (NOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.07 br.s (1H, 7-H), 2.55 m (2H, 11-H), 2.43 t (1H, 9-H, ^3J = 6.6 Hz), 2.33 s [6H, $N(CH_3)_2$], 2.31 br.s (1H, 1-H), 2.28–1.92 m (4H), 1.80 br.s and 1.76 br.s (1H each, 2-H and 6-H), 1.08–1.56 (4H).

***exo*-10-Dimethylaminomethyl-9-aza-*exo*-2,*exo*-6-tricyclo[5.3.1.0^{2,6}]decan-8-one (IV).** Concentrated sulfuric acid, 2 ml, was added dropwise to a mixture of 0.45 g (2 mmol) of oxime **III** and 4 ml of acetonitrile while stirring on a cold water bath (12°C). The mixture was stirred for 4 days at room temperature, carefully poured into a small excess of dilute aqueous sodium hydroxide, and extracted with chloroform. The extract was dried over Na_2SO_4, the solvent was distilled off, and the semicrystalline residue was purified by reprecipitation with ether from anhydrous alcohol. Yield 0.34 g (76%). mp 144–145°C. IR spectrum, ν, cm^{-1}: 3430 (NH); 2970, 2940, 2870, 2830 (C–H); 1660 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.80 br.d (1H, NH), 3.67 m (1H, 10-H, $^3J_{10,12}$ = 6.6 Hz, $^3J_{10,NH}$ = 8.0 Hz, $^3J_{10,1}$ = 2.4 Hz), 2.60 m (2H, 12-H), 2.29 s [6H, $N(CH_3)_2$], 2.22 br.s (1H, 7-H), 2.16 br.d (1H, 1-H, $^3J_{1,10}$ = 2.4 Hz), 2.02 d (1H, *syn*-11-H, ^2J = 9.8 Hz), 1.88–1.98 m (3H), 1.80 br.s and 1.74 br.s (1H each, 2-H and 6-H), 1.12–1.58 m (4H).

REFERENCES

1. Stone, C.A., Torchiana, L.M., and Meckelburg, K.L., *J. Med. Pharm. Chem.*, 1962, no. 5, pp. 665–690.
2. Trojanek, J., Komrsova, M., Pospisek, J., and Cekan, Z., *Collect. Czech. Chem. Commun.*, 1961, vol. 26, no. 11, pp. 2921–2932.
3. Takahashi, T., Fudjimura, H., and Hamashima, Y., *J. Pharm. Soc. Jpn.*, 1964, vol. 84, no. 10, pp. 911–929.
4. Koval'skaya, S.S. and Kozlov, N.G., *Russ. J. Org. Chem.*, 1997, vol. 33, no. 2, pp. 177–182.
5. Koval'skaya, S.S. and Kozlov, N.G., *Russ. J. Org. Chem.*, 2000, vol. 36, no. 6, pp. 785–793.
6. Koval'skaya, S.S. and Kozlov, N.G., *Russ. J. Org. Chem.*, 1998, vol. 34, no. 8, pp. 1131–1135.
7. Koval'skaya, S.S. and Kozlov, N.G., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 4, pp. 499–506.
8. Pashkovskii, F.S., Lakhvich, F.A., Koval'skaya, S.S., and Kozlov, N.G., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 3, pp. 375–381.
9. Vatsuro, K.V. and Mishchenko, G.L., *Imennye reaktsii v organicheskoi khimii* (Name Reactions in Organic Chemistry), Moscow: Khimiya, 1976, pp. 268–269.
10. House, H.O. and Trost, B.M., *J. Org. Chem.*, 1964, vol. 29, no. 6, pp. 1339–1341.
11. Koval'skaya, S.S. and Kozlov, N.G., *Zh. Org. Khim.*, 1992, vol. 28, no. 12, pp. 2496–2502.