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SYNTHESIS OF PYRAZOLINES BASED ON LEVOGLUCOSENONE

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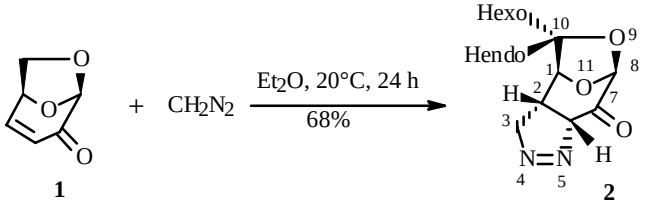
The 1,3-dipolar cycloaddition of diazomethane to levoglucosenone was found to occur regio- and stereoselectively to form optically active 9,11-dioxa-4,5-diazatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one. Levoglucosenone was found to react with methyldiazoacetate to give the 2:1 adduct.

Key words: levoglucosenone, diazomethane, methyldiazoacetate, 1,3-cycloaddition, pyrazoline.

Derivatives of 7,8-diazabicyclo[4.3.0]nonane possess a wide spectrum of biological activity [1-3], for example, pyrazolobenzisoxazoles, psychotropic properties [1]; 6-acetyl-2,2-dimethyl-4-oxa-7,8-diazabicyclo[4.3.0]non-7-en-5-one, vasodilating [2]. 1,3-Dipolar cycloaddition of diazo compounds to a C=C bond is in most instances convenient for synthesizing this class of compounds [4-6].

In continuation of our research on the chemistry of diazo compounds [4] and in order to synthesize new optically active derivatives of 7,8-diazabicyclo[4.3.0]nonane, we studied the reaction of diazomethane and methyldiazoacetate with a sugar enone, levoglucosenone (**1**, 1,6-anhydro-3,4-dideoxy-β-D-pyracosen-2-one), which was prepared in one step from glucose, cellulose, and starch [7-9]. Most conversions involving the C=C bond of **1** are, as a rule, highly regio- and stereoselective because the faces are effectively differentiated during the reaction of **1** with various substrates [9-13] owing to the 1,6-anhydro bridge and the influence of the acetyl oxygens.

We have found that 1,3-dipolar cycloaddition of diazomethane to **1** occurs regio- and stereospecifically at 20°C in Et_2O to form optically active 9,11-dioxa-4,5-diazatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one (**2**, $[\alpha]_D^{20}$ -194°) in 68% yield (Scheme 1). The configuration of **2** was determined by analyzing PMR and ^{13}C NMR spectra (JMOD) using the CHCORR method. Thus, the ^{13}C NMR spectrum exhibits two triplets for methylenes at 68.6 and 83.0 ppm, which are assigned to C-10 and C-3, respectively. The proton chemical shifts were found by using the CHCORR spectrum (Fig. 1). In particular, the C-10 signal at 68.6 ppm in the ^{13}C NMR spectrum couples with the H_2C-10 protons at 3.92 ppm. The C-10 protons have two vicinal spin—spin coupling constants (SSCC) (2.0 and 3.9 Hz) with the C-1 proton. The configuration of the pyrazoline atoms in the heterocycle of **2** was determined by analyzing the PMR spectrum. The SSCC $J_{1,2} = 0$ indicates that the pyrazoline ring is located on the side opposite to the anhydro bridge. The SSCC $J_{2,6} = 10.1$ Hz is consistent with the 1,3-cycloaddition of CH_2N_2 to the C=C bond of **1** occurring *cis*-stereospecifically.



1 **2**

Scheme 1

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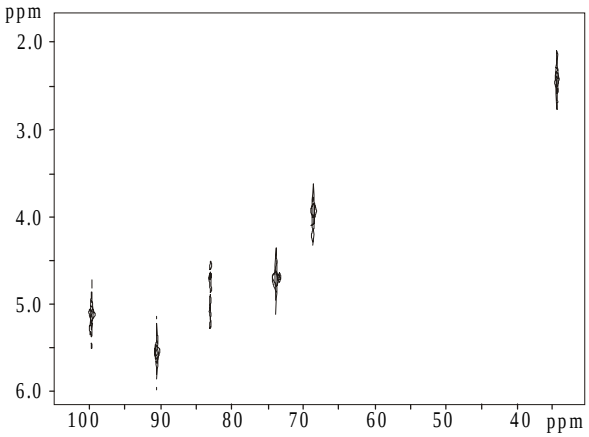
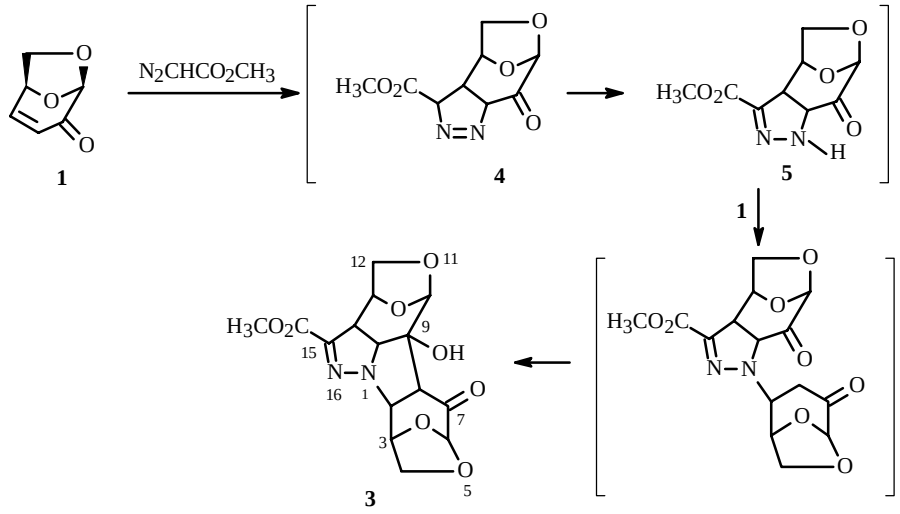


Fig. 1. CHCORR spectrum of 9,11-dioxa-4,5-diazatricyclo[6.2.1.$0^{2,6}$]undec-4-en-7-one (**2**).

Reaction of **1** with methyldiazoacetate in equimolar quantities forms in 93% yield a mixture of two difficultly separated stereoisomers of the 2:1 adducts 9-hydroxy-15-methoxycarbonyl-1,16-diaza-5,11,18,19-tetraoxa-hexacyclo[7.7.1.1^{3,6}.1^{10,13}.0^{2,8}.0^{14,17}]nonadec-15-en-17-ones **3** (Scheme 2). The fact that adducts **3** formed indicates that 1,3-dipolar cycloaddition of methyldiazoacetate to levoglucosenone probably occurs first and leads to the 1-pyrazoline **4**, which then isomerizes into the 2-pyrazoline **5**, which adds to the next molecule of **1** by nucleophilic addition to the electron-deficient olefin. The reaction continues with intramolecular cyclization to form **3** [11]. We used PMR to identify immediately after mixing levoglucosenone and methyldiazoacetate signals (δ 5.22 and 5.71 ppm) corresponding to H-3 and H-6 of the pyrazoline moiety of **4**. These signals disappeared after 24 h.

It should be noted that diazomethane and methyldiazoacetate are extensively decomposed in the presence of catalysts for carbenoid decomposition of diazo compounds such as $Pd(acac)_2$ and $Rh(CF_3CO_2)_4$ [4]. However, products from cyclopropanation of levoglucosenone and **2** and **3** were not observed in the reaction mixture.



Scheme 2

EXPERIMENTAL

IR spectra were recorded as thin layers on Specord M80 spectrometers. ^{13}C and PMR spectra were recorded on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) with TMS internal standard. Melting points were determined on a Boetius microstage. Optical rotation was measured on a Perkin—Elmer 241 MC polarimeter.

1,6-Anhydro-3,4-dideoxy-β-D-pyranosen-2-one (1) [7]. A mixture of cellulose (100 g) and H_3PO_4 (1.5 g) was heated under Ar to 300-350°C. The pyrolyzed fraction was extracted with CH_2Cl_2. The solvent was evaporated. The oil was purified by column chromatography with elution by petroleum ether:ethylacetate (7:3) to afford **1**, 3.4 g, the physicochemical properties of which agreed with the literature [7,8].

9,11-Dioxa-4,5-diazatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one (2) (Fig. 1). A solution of levoglucosenone (0.30 g, 2.4 mmol) in Et_2O (5 mL) was treated with a solution of CH_2N_2 (0.33 g, 8 mmol) (from 0.82 g N-nitroso-N-methylurea) in Et_2O (9 mL) and stirred for 24 h at 20°C. The precipitate was filtered off and washed with a small quantity of Et_2O to afford **2**, 0.27 g (68%), as white crystals with a pink tint, mp 93-95°C (dec.), $[\alpha]_D^{20}$ -194° (*c* 0.10, $CHCl_3$). IR spectrum (ν, cm^{-1}): 2920-2952, 1728 (C=O), 1548 (N=N), 1108 (C–O–C). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.41 (ddd, 1H, *trans*-H-2, J_2 = 0, J_2 = 7.7, J_2 = 10.1, J_2 = 10.1), 3.92 (m, 2H, *exo*-H-10, *endo*-H-10), 4.61 (ddd, 1H, *cis*-H-3, J = 18.2, J_2 = 7.7, J_3 = 2.7), 4.71 (m, 1H, H-1), 5.11 (s, 1H, H-8), 5.15 (dd, 1H, H-3, J = 18.2, J_2 = 10.1), 5.55 (dd, 1H, H-6, J_2 = 10.1, J_3 = 2.7). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 34.5 (C-2), 68.6 (C-10), 73.8 (C-1), 83.0 (C-3), 90.4 (C-6), 99.6 (C-8), 190.3 (C-7). Found (%): C, 48.4; H, 4.5; N, 15.5. $C_7H_8N_2O_3$. Calc. (%): C, 50.0; H, 4.8; N, 16.7.

9-Hydroxy-15-methoxycarbonyl-1,16-diaza-5,11,18,19-tetraoxahexacyclo[7.7.1.1^{3,6}.1^{10,13}.0^{2,8}.0^{14,17}]nonadec-15-en-17-one (3). A solution of **1** (0.10 g, 0.8 mmol) in dry benzene (10 mL) was treated with a solution of methyldiazoacetate (0.11 g, 1.1 mmol) in dry benzene (6 mL), boiled for 48 h, and cooled to -5°C. The precipitate was filtered off and washed with a small amount of Et_2O to afford **3**, 0.13 g (93%), as white crystals, mp 95°C (dec.). IR spectrum (ν, cm^{-1}): 3328 (OH), 3064-2856, 1736, 1704 (C=O), 1560 (N–N), 1460 (C=N), 1136, 1112 (C–O–C). PMR spectrum ($CDCl_3$, δ, ppm): 3.18-3.21 (m, 1H, H-8), 3.35-3.39 (m, 1H, H-14), 3.60-3.63 (m, 2H, H-4), 3.67 (s, 2H, H-12), 3.81 (s, 3H, $COOCH_3$), 4.17-4.21 (m, 1H, H-3), 4.40-4.46 (m, 1H, H-2), 4.60-4.65 (m, 1H, H-13), 4.93 (s, 1H, H-6), 5.07 (s, 1H, H-10). Found (%): C, 51.1; H, 4.8; N, 7.5. $C_{15}H_{17}N_2O_8$. Calc. (%): C, 51.0; H, 4.9; N, 7.93.

REFERENCES

1. R. C. Boruah and J. S. Sandhu, *Synthesis*, **8**, 677 (1982).
2. G. Falsone and B. Spur, *Arch. Pharm. (Weinheim, Ger.)*, **315**, No. 7, 597 (1982).
3. G. A. Conway, L. J. Loeffler, and I. H. Hall, *J. Med. Chem.*, **26**, No. 6, 876 (1983).
4. Yu. V. Tomilov, V. A. Dokichev, U. M. Dzhemilev, and O. M. Nefedov, *Usp. Khim.*, **62**, No. 9, 847 (1993).
5. A. Padwa, ed., *1,3-Dipolar Cycloaddition Chemistry*, J. Wiley & Sons, New York (1984), Vol. 1.
6. A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, New York (1984), Vol. 5.
7. Y. Gelas-Mialhe and J. Gelas, *Carbohydr. Res.*, **199**, 243 (1990).
8. A. Broido, Y. Halpern, and R. Riffer, *J. Org. Chem.*, **38**, 204 (1973).
9. M. S. Miftakhov, F. A. Valeev, and I. N. Gaisina, *Usp. Khim.*, **63**, No. 10, 922 (1994).
10. A. V. Samet, A. N. Yamskov, B. I. Ugrak, and V. V. Semenov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 553 (1997).
11. A. V. Samet and V. V. Semenov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2078 (1997).
12. F. A. Valeev, E. V. Gorobets, and M. S. Miftakhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 152 (1999).
13. E. V. Gorobets, L. V. Spirikhin, I. P. Tsypysheva, M. S. Miftakhov, and F. A. Valeev, *Zh. Org. Khim.*, **8**, 1147 (2001).