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SYNTHESIS OF DIETHYL 8-(DIALKILAMINO)-6-OXO-3-(2-FURIL)-2,4-DICYANOBICYCLO[3.2.1]OCTANE-2,4-DICARBOXYLATES

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As a result of research it was established that the reaction of furfural with secondary amines and ethyl cyanoacetate gave previously unkown diethyl esters of 8-(dialkylamino)-6-oxo-3-(2-furil)-2,4-dicyanobicyclo[3.2.1]octane-2,4-dicarboxylates. Thus, discovered a radically new approach to constructing the bicyclo[3.2.1]octane system, which involves a cascade reaction between furfural and ethyl cyanoacetate in the presence of secondary amines. Structure of all synthesized compounds confirmed by modern physical methods of analysis. By the method of XRD analysis the stereo orientation of substituents in the bicyclic framework is established.

Keywords: *furfural, ethyl cyanoacetate, carbocyclization, bicyclo[3.2.1]octane.*

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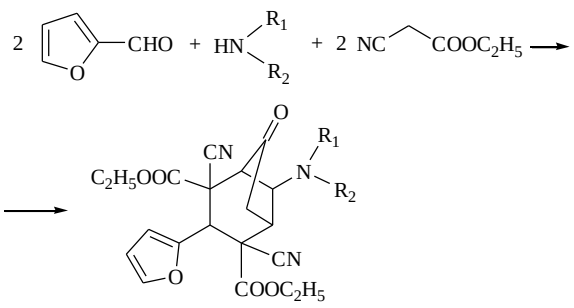
Introduction

Over the past years a lot of publications have appeared on the synthesis of functionally substituted bicyclo[3.2.1]octanes [1–7]. The bicyclo[3.2.1]octane fragment forms the structural basis of a great number of natural terpenes, lignans, and alkaloids. Earlier we discovered a radically new approach to constructing the bicyclo[3.2.1]octane system, which involves a cascade reaction between furfural and isopropyl cyanoacetate in the presence of secondary amines [8].

Results and discussion

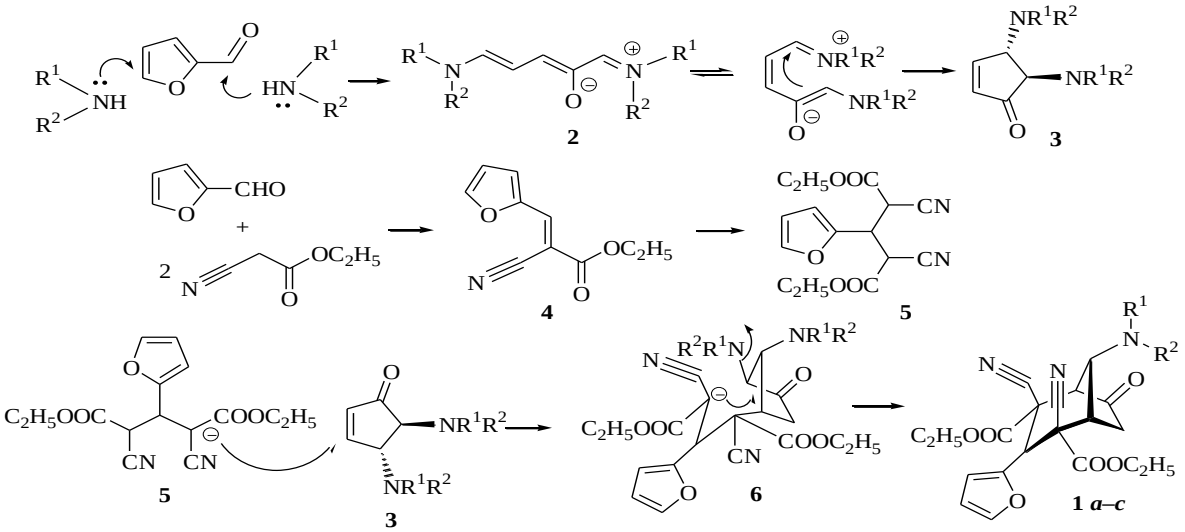
Proceeding with our research synthesized new diethyl esters of 8-(dialkylamino)-6-oxo-3-(2-furil)-2,4-dicyanobicyclo[3.2.1]octane-2,4-dicarboxylic acid (**I *a–c***) (**Scheme 1**).

Scheme 1



a $R_1=R_2=C_2H_5$; *b* $R^1+R^2=(CH_2)_5$; *c* $R^1+R^2=(CH_2)_2O(CH_2)_2$

The proposed reaction mechanism involves the initial formation of a deprotonated Stenhouse salt (**2)** from the secondary amine and furfural (**Scheme 2**).



It should be noted that when furfural and cyanoacetic ester are simultaneously introduced in the reaction medium, the reaction stops at the stage of the formation expected Knoevenagel product3-(2-furyl)-2-cyanoacrylate. We suggest that intermediate (**2)** further undergoes spontaneous 4π-electrocyclization (a Nazarov-type reaction) to form 2,3-diaminocyclopentenones (**3)**. The addition of furfural and ethyl cyanoacetate to the reaction mixture results in the consecutive formation of 3-(2-furyl)-2-cyanoacrylate (**4**) and Michael adduct (**5**). Compound (**5**) in the basic medium undergoes a Michael addition to cyclopentenone (**3**) followed by carbocyclization of the resulting adduct (**6**), probably, via nucleophilic elimination of the secondary amine.The structure of compounds (**1*a*–*c*)** is confirmed by the methods IR-, NMR and mass spectrometry and elemental analysis, as well as the XRD analysis of compound **1c** (F**igures 1–3**).

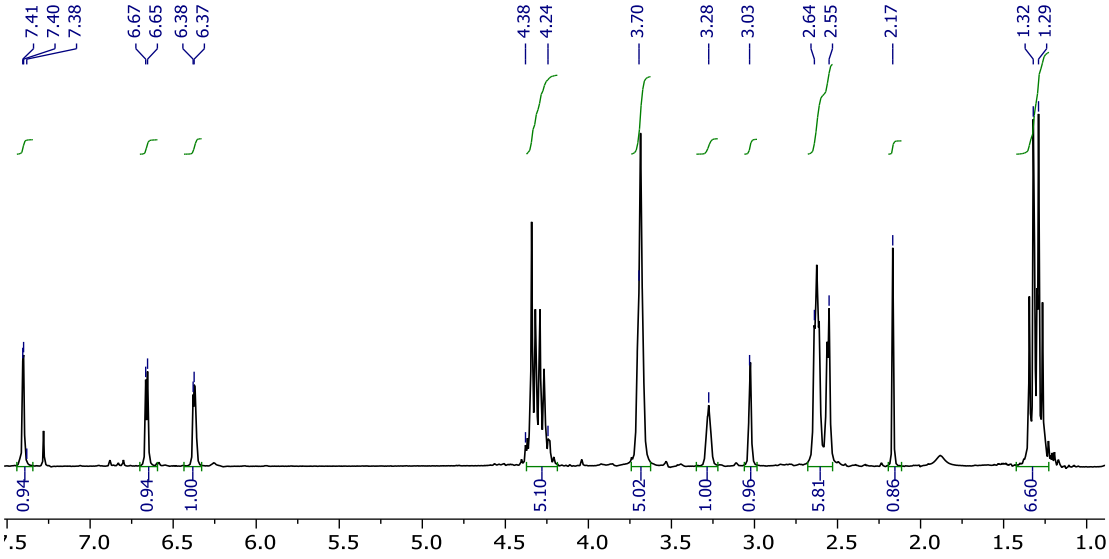


Fig. 1. ^{1}H NMR spectrum of diethyl 8-morpholino-6-oxo- 3-(2-furyl)-2,4-dicyanobicyclo [3.2.1]octane-2,4-dicarboxylate (**1*c***).

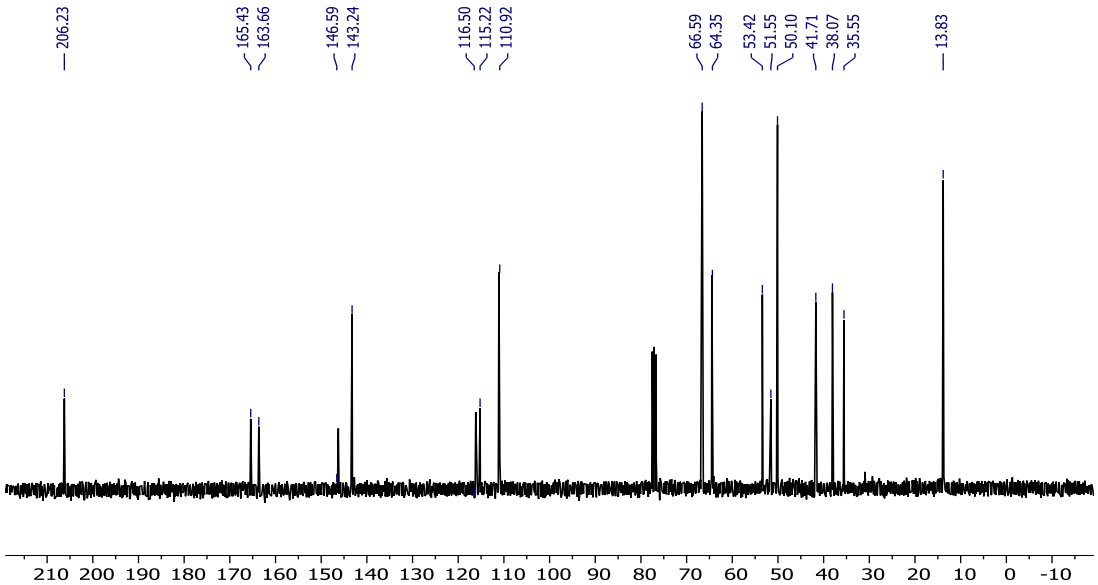


Fig. 2. ^{13}C NMR spectrum of diethyl 8-morpholino-6-oxo-3-(2-furyl)-2,4-dicyano-bicyclo[3.2.1]octane-2,4-dicarboxylate (**1*c***).

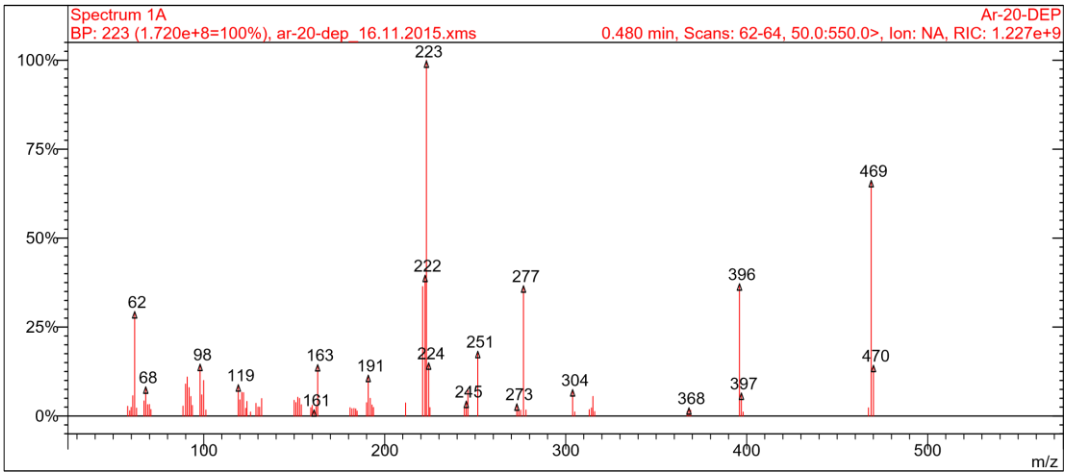


Fig. 3. Mass-spektrum of diethyl 8-morpholino-6-oxo-3-(2-furyl)-2,4-dicyano-bicyclo[3.2.1]-octane-2,4-dicarboxylate (**1*c***).

Crystallographic data. Crystals for X-ray diffraction study were obtained by slow evaporation of saturated ethanol solution. The crystals of $C_{24}H_{27}N_3O_7$ are monoclinic. At 293 K a = 8.5867(6), b = 32.281(2), c = 8.7824(6) Å, β = 105.9240(10)^0, V = 2341.0(3) Å^3, Mr = 469.49, Z = 4, space group $P2_1/n$, d_{calc}= 1.332 g/cm^3, μ(MoK_α-radiation) = 0.099 mm^{-1}, F(000) = 992. Intensity of 26806 reflection (5796 independent, R_{int}=0.052) were measured on the Brucker SMART APEXII CCD diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\theta_{max}$ = 57^0). The structure was solved by direct method using SHELXTL package **[**9**]**.

Positions of the hydrogen atoms were located from electron density difference maps and refined by ″riding″ model with U_{iso} = 1.2U_{eq} of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms (309 parameters) using 5796 reflections was converged to wR2 = 0.179 (R1 = 0.066 for 3866 reflections with F>4σ(F), S = 1.049). The final atomic coordinates, and crystallographic data for molecule **1*c*** have been deposited to with the Cambridge Crystallographic Data Centre and are available on request quoting the deposition numbers CCDC 1023258 (Figure 4).

Results of X-ray diffraction study demonstrated that bicyclic framework of molecule adopt typical chair-envelope conformation. The deviation of the C5 and C8 atoms

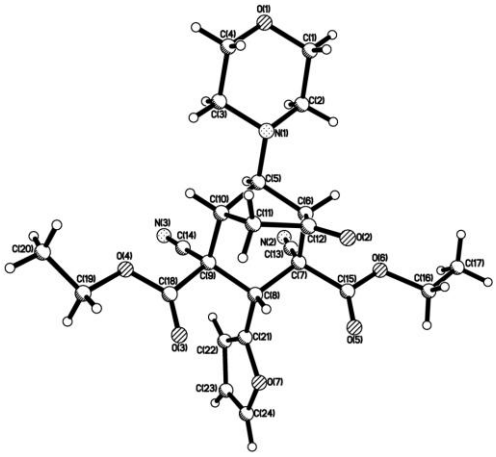


Fig. 4. Molecular structure of (1S,2S,3S,4R,5R, 8S)diethyl 2,4-dicyano-3-(furan-2-yl)-8-morpholino-6-oxobicyclo[3.2.1]octane-2,4-dicarboxylate according to X-ray diffraction data.

of cyclohexane ring and the C5 atom of cyclopentanone ring from remaining atoms of rings are –0.88 Å, 0.57 Å and –0.71 Å, respectively. The morpholine ring has chair conformation (deviation of the N1 and O1 atoms from mean plane of carbon atoms of ring are –0.68 Å and 0.62 Å, respectively) are oriented towards cyclopentanone ring of bicyclic fragment and it is located almost symmetrically with respect to the C5 methylene bridged group (the C6-C5-N1-C2 and C10-C5-N1-C3 torsion angles are 67.9(2)^0 and -62.1(2)^0, respectively). All bulky substituents in cyclohexane ring of bicyclic fragment adopt an equatorial orientation while smaller cyano groups gave axial orientation. Values of relevanet torsion angles are: C7-C8-C9-C18 –163.4(2)^0, C9-C8-C7-C15 161.6(2)^0,

C10-C9-C8-C21 –175.0(2)^0, C7-C8-C9-C14 77.5(2)^0, C9-C8-C7-C13 –76.9(2)^0. Both carbethoxy substituents have antiperiplanar conformation (the C15-O6-C16-C17 and C18-O4-C19-C20 torsion angles are 162.2(3)^0 and 174.8(3)^0, respectively. The furan ring is almost co-planar to the C8-H bond (the H-C8-C21-O7 torsion angle is 10^0) [10].

Thus, we discovered a new cascade reaction which allow a one-pot synthesis of diethyl 8-(dialkylamino)-6-oxo-3-(2-furyl)-2,4-dicyanobicyclo-[3.2.1]octane-2,4-dicarboxylates from accessible reagents.

Experimental part

Allcommercially available chemicals were obtained from Merc and Sigma-Aldrich companies without further purification. The IR spectra were run on a Varian 3600 FT-IR Excalibur Series FTIR spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-300 MHs spectrometer at 300 and 75 MHs, respectively. Elemental analysis for C, H, and N was performed on a Carlo Erba 1106 analyzer. The melting points were measured on a Kofler hot stage. The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates, eluent–acetone–hexane (1:1), development in iodine vapor, UV detector.

Diethyl 8-(dialkylamino)-6-oxo-3-(2-furyl)2,4-dicyanobicyclo-[3.2.1]octane-2,4-dicarboxylates (1*a*-*c*).

A mixture of 0.01 mol of furfural and 0.02 mol of a secondary amine (Et_2NH, piperidine or morpholine) was stirred in 15 mL of 96% ethanol for 1 h. A mixture of 0.01 mol of furfural and 0.02 mol of ethyl cyanoacetate was added to the resulting solution, and the reaction mixture was allowed to stand for 24 h. The precipitate was filtered off and dried.

Diethyl 8-diethylamino-6-oxo-3-(2-furyl)-2,4-dicyanobicyclo[3.2.1]octane-2,4-dicarboxylate (1a), yield – 42 %, ivory crystals, m.p. – 147^{0}C (EtOH).

IR spectrum, ν, cm^{-1}: 2240 (C≡N), 1750 (C=O), 1654 (COO).

^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.68–0.73 (t, 3H, CH_3), 0.89–0.93 (t, 3H, CH_3), 2.55–2.58 (m, 2H, CH_2), 2.69–2.73 (q, 4H, N–CH_2), 2.97 (br.s, 1H, CH), 3.17–3.20 (d, 1H, CH), 4.01 (s, 1H, CH), 4.27–4.35 (m, 5H, 2OCH_2, CH), 6.34 (d., 1H^{4}furil), 6.67 (d, 1H, H^{3}furyl), 7.35–7.36 (d, 1H, H^5 furyl).

^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 6.52, 9.26, 31.19, 33.46, 37.57, 37.99, 45.60, 47.03, 50.00, 58.60, 59.65, 106.30, 106.39, 110.79, 111.72, 138.57, 141.92, 159.32, 161.05, 202.43.

Found, %: C 63.32, H 6.57, N 9.30. $C_{24}H_{29}N_3O_6$. Calculated, %: C 63.28, H 6.42, N 9.22

Diethyl 8-(piperidin-1-yl)-6-oxo-3-(2-furyl)-2,4-dicyanobicyclo[3.2.1]octane-2,4-dicarboxylate (1*b*), yield – 49 %, ivory crystals, m.p. – 161^{0}C (EtOH).

IR spectrum, ν, cm^{-1}: 2240 (C≡N), 1750 (C=O), 1654 (COO).

^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 1.26–1.34 (t, 6H, 2CH_3), 1.49–1.55 (m, 6H, CH_2), 2.52–2.57 (m, 6H, 2N–CH_2, CH_2), 3.05 (s, 1 H, CH), 3.28–3.30 (d, 1H, CH), 3.66 (s, 1H, CH), 4.24–4.32 (m, 5H, 2OCH_2, CH), 6.33–6.34 (d, 1H, H^{4}f uryl), 6.65(d, 1H, H^{3}furyl), 7.35–7.36 (d, 1H, H^{5}furyl).

^{13}C NMR spectrum (75 MHz, $CDCl_3$), δC, ppm: 9.26, 19.58, 21.08, 31.07, 33.42, 37.60, 46.12, 47.19, 49.43, 59.77, 62.72, 106.39, 110.79, 111.74, 138.55, 141.93, 159.24, 160.99, 202.25.

Found, %: C 64.39, H 6.37, N 9.11. $C_{25}H_{29}N_3O_6$. Calculated, %: C 64.23, H 6.25, N 8.99.

Diethyl 8-morpholino-6-oxo-3-(2-furyl)-2,4-dicyanobicyclo[3.2.1]octane-2,4-dicarboxylate (1c), yield 45 %, ivory crystals, m.p. 216^{0}C (EtOH).

IR spectrum, ν, cm^{-1}: 2240 (C≡N), 1750 (C=O), 1654 (COO).

1H-NMRspectrum (300 MHz, $CDCl_3$), δ, ppm: 1.27–1.35 (t, 6H, 2CH_3), 2.56 (d, 1H, CH), 2.63 (t, 4H, 2N–CH_2), 3.03 (s, 1H, CH), 3.28 (s, 1H, CH), 3.70 (m, 5H, 2OCH_2, CH), 4.27–4.32(m, 5H, 2OCH_2, CH); 6.33–6.34 (d, 1H, H^{4}furyl), 6.65(d , 1H, H^{3}furyl), 7.35–7.36 (d, 1H, H^{5}furyl).

^{13}C NMR spectrum (75 MHz, $CDCl_3$), δC, ppm: 9.25, 31.00, 33.50, 37.13, 45.52,

46.97, 48.84, 59.90, 62.01, 106.34, 110.64, 111.59, 138.66, 141.66, 159.08, 160.85, 202.00.

Found, %: C 61.59, H 5.97, N 9.11. $C_{24}H_{27}N_3O_7$. Calculated, %: C 61.40, H 5.80, N 8.95.

References

1. Lefranc A., Gremaud L., Alexakis A. Construction of bicyclo[3.2.1]octanes with four stereogenic centers by organocatalytic domino Michael/aldol reaction. Org. Lett. 2014. V. 16. No 20. P. 5242–5245.
2. Rueping M., Kuenkel A., Tato F., Bats J.W. Asymmetric organocatalytic domino Michael/Aldol reactions: enantioselective synthesis of chiral cycloheptanones, tetrahydrochromenones, and polyfunctionalized bicycle [3.2.1] octanes. Angew. Chem. Int. Ed., 2009. V. 48. P. 3699–3702.
3. Tan B., Lu Y., Zeng X., Chua P.J., Zhong G. Facile domino access to chiral bicyclo[3.2.1]octanes and discovery of a new catalytic activation mode. Org. Lett. 2010. V. 12. No 12. P. 2682–2685.
4. Zhao J., Yang S., Xie X., Li X., Liu Y. Ligand-effect in gold(I)-catalyzed rautenstrauch rearrangement: regio- and stereoselective synthesis of bicyclo[3.2.1]octa-3,6-dienes through cyclodimerization of 1-ethynyl-2-propenyl esters. J. Org. Chem., 2018. V. 83. No 3. P. 1287–1297.
5. He C., Bai Z., Hu J., Wang B., Xie H., Yu L., Ding H. A divergent [5+2] cascade approach to bicyclo[3.2.1]octanes: facile synthesis of entkaurene and cedrene-type skeletons. Chem. Communications. 2017. V. 53. No. 60. P. 8435–8438.
6. Takatori K., Ota S., Tendo K., Matsunaga K., Nagasawa K., Watanabe S., Nagaoka H. Synthesis of methylen S.ebicyclo[3.2.1]octanol by a Sm(II)-induced 1,2-rearrangement reaction with ring expansion of methylenebicyclo[4.2.0]octanone. Org. Lett. 2017. V. 19. No 14. P. 3763–3766.
7. Presset M., Coquerel Y., Rodriguez J. Syntheses and applications of functionalizd bicyclo[3.2.1]octanes: thirteen years of progress. Chem. Rev., 2013. V. 113. No 1. P. 525−595.
8. Ismiev A.I., Dotsenko V.V., Aksenov N.A., Mamedova G.Z., Magerramov A.M. A new synthetic approach to functionalized bicyclo[3.2.1]octanes. Russian Journal of General Chem. 2018. V. 88. No 7. P. 1533–1536.
9. Sheldrick G.M. A short history of SHELX. Acta Crystallogr. 2008. Sect A, A 64. P. 112–122.
10. Shishkina S.V., Shishkin O.V., Medviediev V.V., Omelchenko I.V., Ismiev A.I., Magerramov A.M. Weak but strong: role of weak C–H…X (X=O, N) hydrogen bonds in organization of crystals of (1S,2S,3S,4R,5R,8S)-diethyl-2,4-dicyano-3-(furan-2-yl)-8-morpholino-6-oxo-bicyclo[3.2.1]octane-2,4-dicarboxylate. Struct. Chem. 2016. V. 27. No 1. P. 315–321.

DİETİL-8-(DİALKİLAMINO)-6-OKSO-3-(2-FURİL)-2,4-DİSİANOBİTSİKLO[3.2.1]OKTAN-2,4-DİKARBOKSİLATLARIN SİNTEZİ

A.İ.İsmiyev

Aparılan tədqiqatlar nəticəsində müəyyən edilmişdir ki, furfurolun ikili aminlər və etilsianasetat ilə reaksiyası əvvəllər məlum olmayan 8-(dialkilamin)-6-okso-3-(2-furil)-2,4-disianbitsiklo[3.2.1]oktan-2,4-dikarboksilatların alınması ilə nəticələnir. Beləliklə, furfurolun etilsianasetatla ikili aminlər iştirakında kaskad karbotsiklləşməsinə əsaslanan bitsiklo[3.2.1]oktan sisteminin alınması üçün prinsipcə yeni yanaşma aşkar edilmişdir. Bütün sintez edilmiş maddələrin quruluşu müasir fiziki tədqiqat üsulları ilə təsdiq edilmişdir. RQA üsulu ilə bitsiklik karkasda olan əvəzedicilərin stereo istiqamətliliyi müəyyən olunmuşdur.

Açar sözlər: *furtural, etilsianasetat, karbotsiklləşmə, bitsiklo[3.2.1]oktan.*

СИНТЕЗ ДИЭТИЛ-8-(ДИАЛКИЛАМИНО)-6-ОКСО-3-(2-ФУРИЛ)-2,4-ДИЦИАНОБИЦИКЛО[3.2.1]ОКТАН-2,4-ДИКАРБОКСИЛАТОВ

А.И.Исмиев

В результате проведенных исследований установлено, что реакция фурфурола с вторичными аминами и этилцианацетатом приводит к ранее неизветстным диэтиловым эфирам 8-(диалкиламино)-6-оксо-3-(2-фурил)-2,4-дицианобицикло[3.2.1]октана-2,4-дикарбоксилатам. Это означает, что нами обнаружен принципиально новый подход к построению бицикло[3.2.1]октановой системы, основанный на изящной каскадной реакции между фурфуролом и изопропил-цианоацетатом в присутствии вторичных аминов. Строение всех синтезированных соединений доказана современными физическими методами анализа. Методом РСА установлена стереоориентация заместителей в бициклическом каркасе.

Ключевые слова: *фурфурал, этилцианацетат, карбоциклизация, бицикло[3.2.1]октан.*