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Cyclocondensation of 1,5-Substituted 7-Amino-Tetrahydro-1,5-Benzodiazepin-2-Ones with α,β-Unsaturated Ketones

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Abstrsct: **The interaction of 7-amino-4-methyl-1-R^1-5-R^2-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones with α,β-unsaturated ketones – dimethyl-2-oxoglutaconate and methyl-4-oxo-2-pentenoate was investigated in the conditions of the modified Doebner-Miller reaction. Four-membered derivatives of the new fused heterosystem – 4,8-dioxo-6,7,8,9-tetrahydro-4H-[1,4]diazepino[3,2,1-hi]pyrido[4,3,2-cd]indole were synthesized by the condensation of 7-amino-4-methyl-1-R^1-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones (5-R^2 = H) with dimethyl-2-oxoglutaconate. By the interaction of 7-amino-4-methyl-5-alkyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones with oxoglutaconate, tricyclic 2-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[2,3-g]quinolines were obtained. The reaction of 7-amino-1-methyl(or 5-methyl)-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones and methyl-4-oxopentenoate occured to form 10-methylsubstituted [1,4]diazepino[2,3-g]quinoline derivatives. It was established that the direction of cyclization and the structure of the polycyclic products depend on the presence of substituents at the 1- and 5-positions of starting amines and on the structure of α, β-unsaturated ketone.**

Keywords: **7-amino-1,5-benzodiazepin-2-ones, quinolines, Doebner-von Miller reaction, α,β-unsaturated ketones, cyclocondensation**

I. Introduction

Some polycyclic benzodiazepines and quinolines are known to possess miscellaneous biological activity [1-3]. Numerous papers have described the synthesis of polycyclic 1,5-benzodiazepine derivatives with a pyridine ring annelated to the heptatomic diazepine nucleus [4]. As a continuation of our interest in polycyclic 1,5-benzodiazepines we investigated the combination of the diazepine and quinoline heterocycles in the common polyheterocyclic system where the pyridine ring is annelated to the aromatic ring of bicyclic benzodiazepine.

The modified Doebner-von Miller synthesis is one of the pathways to the quinoline ring system [2,3]. The key substrates for this condensation reaction are aromatic amines and α,β-unsaturated ketones. In the present paper, we report our results on the preparation of tetracyclic diazepinopyridoindoles and tricyclic diazepinoquinolines.

II. Results and discussion

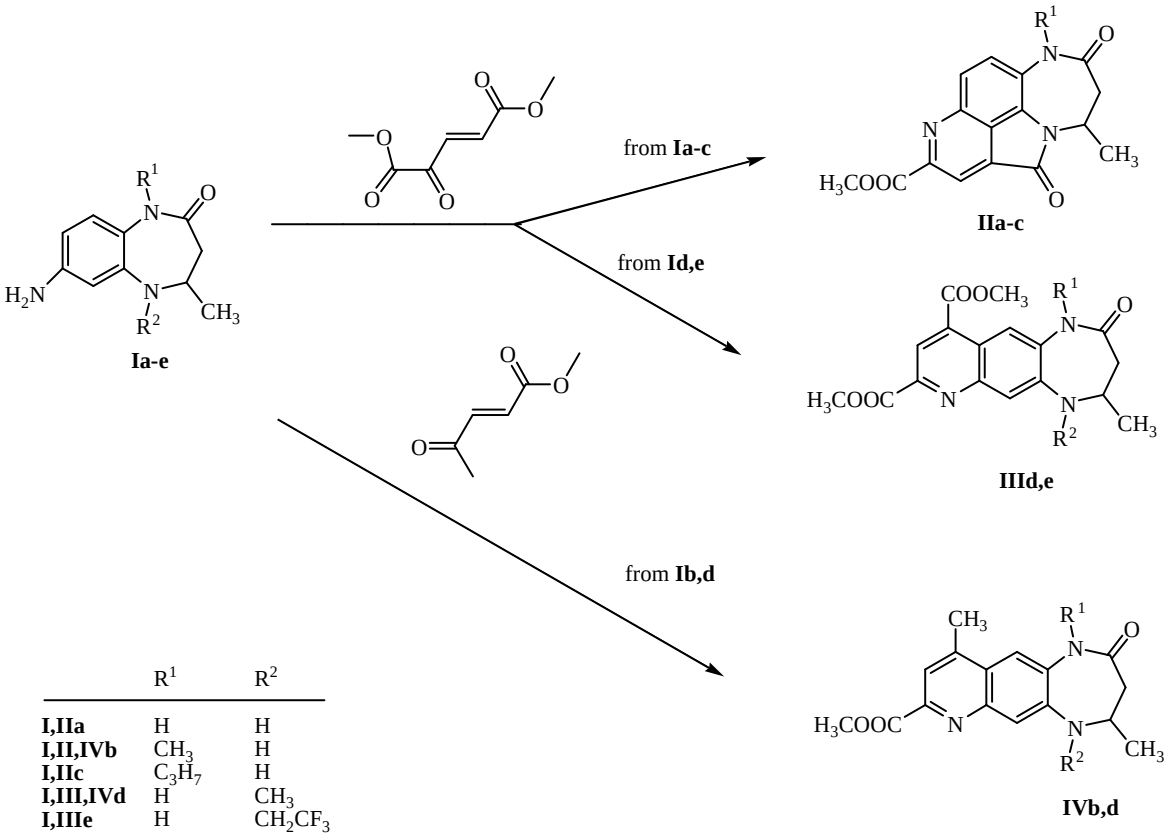
In this study, 7-amino-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **Ia-e** were used as starting amine components to prepare annelated derivatives (Scheme 1). Cyclocondensation was accomplished by the reaction of amines with dimethyl-2-oxoglutaconate and methyl-4-oxo-2-pentenoate (modified Doebner-von Miller sequence) in a single step [3,5]. Thus, the treatment of amines **Ia-e** with 1.5 equiv of unsaturated ketone in dichloromethane at room temperature for 24 h and then for additional 24 h after the addition of 3*M* hydrogen chloride solution in glacial acetic acid gave cyclic derivatives **IIa-c, IIId,e, IVb,d**. The yields of compounds ranged from poor to moderate (16-51%).

For the application of this cyclization methodology, first we employed amines **Ia-c** which did not possess an alkyl group on the N_5 atom of the heterocyclic diazepine ring. The reaction of **Ia-c** with dimethyl-2-oxoglutaconate afforded tetracyclic tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole derivatives **IIa-c**. During the first stage of this reaction, the amino group added to the carbon atom of unsaturated ketone at *β*-position with respect to the ketonic function and cyclization occurred to give the cyclized piperidinol [3]. The addition of the acid catalyst effected the dehydration and aromatization of the latter together with intramolecular acylation of the diazepine ring N_5 atom by the cyclic ester group and an indole ring was formed [6]. The pyridine ring closure in 7-aminoderivatives **Ia-c** took place at the 6-position of the benzodiazepine moiety.

When 7-amino-5-alkyl-substituted benzodiazepinones **Id,e** were treated with oxoglutaconate, the cyclocondensation proceeded at the 8-position of the bicyclic heterocycle and linear tricyclic diazepinoquinolines **IIId,e** were obtained. The TLC analysis did not indicate the formation of isomeric products.

Interaction of 7-amino-1-methyl(or 5-methyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **Ib,d** with methyl-4-oxo-2-pentenoate gave only 10-methylsubstituted [1,4]diazepino[2,3-*g*]quinolines **IVb,d**, i.e, cyclization took place at the 8-position of starting amines. The position of substituents in the pyridine cycle of compounds **IVb,d** confirmed over again that the first step of cyclocondensation reaction is the addition of a primary amino group to the carbon atom of unsaturated ketone. It is noteworthy that interaction of **Ib** with glutaconate gave four-membered indole derivative **IIb**. The change of the reaction direction is supposedly related with the steric effect of methyl group. The cyclization at the 6-position of benzene nucleus does not take place due to the relatively large steric volume of methyl group.

Scheme 1



	R^1	R^2
I,IIa	H	H
I,II,IVb	CH_3	H
I,IIc	C_3H_7	H
I,III,IVd	H	CH_3
I,IIIe	H	CH_2CF_3

The synthesis of the starting materials **Ia** [7] and **Id** [8] was described in our previous studies. Derivatives **Ib,c,e** were then easily obtained from the corresponding nitroderivatives **Vb,c,e** by catalytic hydrogenation. 1,4-Dimethyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**Vb**) and 4-methyl-7-nitro-5-(2,2,2-trifluorethyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**Ve**) were prepared according to the procedure described in our previous work [9]. Compound **Vc** was synthesized by alkylation of 4-methyl-7-nitro-1,3,4,5,-tetrahydro-2*H*-1,5-benzodiazepin-2-one [10] with 1-bromopropane under phase-transfer catalysis conditions. The starting aminobenzodiazepinones carrying various alkyl groups at the N_1 and N_5 atoms of the diazepine heterocycle ring were chosen for their acute solubility in organic solvents.

The structures attributed to the compounds described in this paper are consistent with the results of elemental analysis, IR, ^{1}H NMR spectral data. In this connection, the ^{1}H NMR spectra of linear and angular condensed regioisomeric systems are particularly significant. The signals of two benzene ring protons form two doublets or two singlets for compounds **IIa-c** and **IIId,e, IVb,d**, respectively. These assignments are unambiguously confirmed when NOE is observed between amide group (N–H) or methyl group (N–CH_3) protons and the nearest benzene ring proton (16-25% and 11-24%, respectively).

The quinoline derivatives are highly colored compounds and ethanolic solutions of **IIId,e** exhibit deep colors accompanied with fluorescence.

Generally, we have described the synthesis of novel heterocyclic systems from variously N_1- and N_5-substituted amino-1,5-benzodiazepinones employing the Doebner-von Miller quinoline synthesis. It was confirmed that the formation of a new pyridine ring took place at the adjacent position with respect to the primary amine group of the starting compound. However, the regiochemical outcome of cyclization reaction for asymmetrically substituted aromatic amines was unpredictable [3,11]. Our studies showed that the direction of cyclocondensation reaction depended on the substituents at the 1- and 5-positions of seven-membered heterocycle and on the structure of the α,β-unsaturated ketone.

III. EXPERIMENTAL

Melting points were determined in open capillaries method on a MEL-TEMP 1202D apparatus and are uncorrected. The IR spectra (potassium bromide) were taken on a Perkin Elmer Spectrum GX FT-IR spectrometer. ^{1}H (300 MHz) NMR spectra were recorded in deuteriochloroform on a Varian Unity Inova 300 spectrometer at 302 K. The chemical shifts are referenced to tetramethylsilane (δ (^{1}H) = 0). The values of chemical shifts are expressed in ppm and coupling constants (*J*) in Hz. The reactions were controlled by the TLC method and performed on a Merck precoated silica gel aluminum roll ($60F_{254}$) with chloroform-ethyl acetate-methanol (v/v, 14:7:1) as the eluent and was visualized with UV light. Dry column vacuum chromatography [12] was performed with silica gel Chemapol L 5/40 mesh.

Dimethyl-2-oxoglutaconate was synthesized from 2-oxoglutaric acid according to [5], methyl-4-oxo-2-pentenoate was synthesized analogically from 3-bromolevulinic acid methyl ester [13].

General Procedure for the Synthesis of **IIa–c, IIId,e, IVb,d**. To a stirred solution of the appropriate aminobenzodiazepinone **Ia-e** (5.0 mmol) in 100-300 ml of dry dichloromethane, 1.28 g (7.5 mmol) of dimethyl-2-oxoglutaconate or 0.96 g (7.5 mmol) of methyl-4-oxo-2-pentenoate was added. The mixture was stirred at room temperature for 24 h. Then 4 ml (12.0 mmol) of 3*M* hydrogen chloride solution in glacial acetic acid was added and the intensively colored mixture was stirred at room temperature for additional 24 h. In some occasions, the precipitate was formed. The mixture was treated with a saturated aqueous sodium hydrogencarbonate solution until the aqueous phase became alkaline (*p*H 7-8), then the organic phase was washed with water. After drying over magnesium sulfate and the removal of the solvent in vacuum, the dark semi-solid residue was subjected to purification. Recrystallization from a proper solvent gave pure compounds **IIId,e** and **IVb,d**. Dark oily residues were subjected to dry column vacuum chromatography (silicagel) using the dichloroethane-ethyl acetate system for gradient elution. Organic fractions with R_f ~0.35 were collected and after removal of the solvent gave compounds **IIa-c**. Pure compounds were obtained by recrystallization from a proper solvent.

Methyl 6-methyl-4,8-dioxo-6,7,8,9-tetrahydro-4H-[1,4]diazepino[3,2,1-hi]pyrido[4,3,2-cd]indole-2-carboxylate **(IIa)**

Brightly yellow crystals (chloroform, 30% yield), mp 299-302 °C [6].

Methyl 6,9-dimethyl-4,8-dioxo-6,7,8,9-tetrahydro-4H-[1,4]diazepino[3,2,1-hi]pyrido[4,3,2-cd]indole-2-carboxylate **(IIb)**

Orange crystals (chloroform, 29% yield), mp 231-233 °C [6].

Methyl 6-methyl-4,8-dioxo-9-propyl-6,7,8,9-tetrahydro-4H-[1,4]diazepino[3,2,1-hi]pyrido[4,3,2-cd]indole-2-carboxylate **(IIc)**

Orange crystals (mixture of diethyl ether and ethyl acetate, yield 25%), mp 163-165 °C; IR: 1725, 1702, 1660 cm^{-1}; ^{1}H NMR: δ 1.00 (t, *J* = 7.4 Hz, 3H, CH_3), 1.49 (d, *J* = 6.7 Hz, 3H, CH_3), 1.65-1.89 (m, 2H, CH_2), 2.99 (dd, *J* = 2.4, 14.0 Hz, 1H, CH_2), 3.13 (dd, *J* = 5.4, 13.9 Hz, 1H, CH_2), 3.96-4.12 (m, 2H, CH_2), 4.13 (s, 3H, OCH_3), 4.89 (m, 1H, CH), 7.64 (d, *J* = 9.4 Hz, 1H, 10-H), 8.00 (d, *J* = 9.4 Hz, 1H, 11-H), 8.72 (s, 1H, 3-H). *Anal.* Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.30; H, 5.31; N, 11.64.

Dimethyl 4,5-dimethyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[2,3-g]quinoline-8,10-dicarboxylate **(IIId)**

Yellow crystals (ethyl acetate, 46% yield), mp 203-205 °C; IR: 3319, 3196, 1723, 1670 cm^{-1}; ^{1}H NMR: δ 1.31 (d, *J* = 6.1 Hz, 3H, CH_3), 2.44 (dd, *J* = 8.9, 13.4 Hz, 1H, CH_2), 2.72 (dd, *J* = 4.8, 13.4 Hz, 1H, CH_2), 3.02 (s, 3H, CH_3), 3.94 (m, 1H, CH), 4.06 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 7.83 (s, 1H, 6-H), 8.49 (s, 1H, 11-H), 8.59 (s, 1H, 9-H), 8.67 (br s, 1H, NH). *Anal.* Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.64; H, 5.30; N, 11.90.

Dimethyl 4-methyl-2-oxo-5-(2,2,2-trifluorethyl)-2,3,4,5-tetrahydro-1H-[1,4]diazepino[2,3-g]quinoline-8,10-dicarboxylate **(IIIe)**

Yellow crystals (ethyl acetate, 51% yield), mp 236-238 °C; IR: 3320, 1745, 1727, 1693 cm^{-1}; ^{1}H NMR: δ 1.21 (d, *J* = 6.1 Hz, 3H, CH_3), 2.36 (dd, *J* = 11.3, 13.4 Hz, 1H, CH_2), 2.61 (ddd, *J* = 1.4, 5.4, 13.4 Hz, 1H, CH_2), 3.78 (m, 1H, CH), 4.06 (s, 3H, OCH_3), 4.06-4.20 (m, 2H, 5-CH_2), 4.10 (s, 3H, OCH_3), 8.06 (s, 1H, 6-H), 8.44 (br s, 1H, NH), 8.60 (s, 1H, 11-H), 8.67 (s, 1H, 9-H). *Anal.* Calcd. for $C_{19}H_{18}F_3N_3O_5$: C, 53.65; H, 4.27; N, 9.88. Found: C, 53.48; H, 4.36; N, 10.01.

Methyl 1,4,10-trimethyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[2,3-g]quinoline-8-carboxylate **(IVb)**

Yellow crystals (diethyl ether, 33% yield), mp 223-225 °C; ^{1}H NMR: δ 1.32 (d, *J* = 6.2 Hz, 3H, 4-CH_3), 2.35 (dd, *J* = 8.0, 13.1 Hz, 1H, CH_2), 2.63 (dd, *J* = 5.2, 13.1 Hz, 1H, CH_2), 2.73 (d, *J* = 0.8 Hz, 3H, 10-CH_3), 3.52 (s, 3H, 1-CH_3), 3.7 (br s, 1H, NH), 4.06 (s, 3H, 8-CH_3), 4.10 (m, 1H, CH), 7.69 (s, 1H, 6-H), 7.70 (s, 1H, 11-H), 7.96 (q, *J* = 0.8 Hz, 1H, 9-H). *Anal.* Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.02; H, 6.08; N, 13.49.

Methyl 4,5,10-trimethyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[2,3-g]quinoline-8-carboxylate **(IVd)**

Yellow crystals (ethyl acetate, 35% yield), mp 228-230 °C; ^{1}H NMR: δ 1.25 (d, *J* = 6.2 Hz, 3H, 4-CH_3), 2.39 (dd, *J* = 9.4, 13.2 Hz, 1H, CH_2), 2.65 (ddd, *J* = 1.1, 5.2, 13.2 Hz, 1H, CH_2), 2.72 (d, *J* = 0.8 Hz, 3H, 10-CH_3), 3.00 (s, 3H, 5-CH_3), 4.08 (s, 3H, 8-CH_3), 7.54 (s, 1H, 11-H), 7.83 (s, 1H, 6-H), 7.95 (q, *J* = 0.8 Hz, 1H, 9-H), 8.48 (br s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.30; H, 6.17; N, 13.33.

General procedure for the synthesis of **Ib,c,e**. In a hydrogenation apparatus, equipped with a magnetic stirrer, the catalyst 10% palladium on carbon (10% of the weight of the starting nitroderivative) was added to a solution of suitable nitrobenzodiazepinone **Vb,c,e** (20.0 mmol) in 150-200 ml of methanol and the mixture was hydrogenated at room temperature and atmospheric pressure. After the consumption of 1.34 l (60 mmol) of hydrogen the catalyst was filtered off. The filtrate was concentrated to dryness in vacuum and the resultant solid residue was crystallized from a proper solvent.

7-Amino-1,4-dimethyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one **(Ib)**

Synthesized from **Vb** [9]. Yellowish crystals (ethyl acetate, 77% yield), mp 149-151 °C; ^{1}H NMR: δ 1.24 (d, *J* = 6.2 Hz, 3H, CH_3), 2.28 (dd, *J* = 7.7, 12.7 Hz, 1H, 3-CH_2), 2.51 (dd, *J* = 5.2, 12.6 Hz, 1H, 3-CH_2), 3.13 (br s, 1H, NH), 3.28 (s, 3H, 1-CH_3), 3.66 (br s, 2H, NH_2), 4.00 (m, 1H, CH), 6.18 (d, *J* = 2.5 Hz, 1H, 6-H), 6.36 (dd, *J* = 2.5, 8.4 Hz, 1H, 8-H), 6.91 (d, *J* = 8.4 Hz, 1H, 9-H). *Anal.* Calcd. for $C_{11}H_{15}N_3O$: C, 64.34; H, 7.37; N, 20.47. Found: C, 64.38; H, 7.30; N, 20.66.

7-Amino-4-methyl-1-propyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one **(Ic)**

Synthesized from **Vc**. Beige colored crystals (mixture of methanol and diethyl ether, 71% yield), mp 143-145 °C; IR: 3407, 3345, 3330, 3233, 1666-1609 cm^{-1}; ^{1}H NMR: δ 0.84 (t, *J* = 7.4 Hz, 3H, CH_3), 1.23 (d, *J* = 6.2 Hz, 3H, CH_3), 1.50 (m, 2H, CH_2), 2.23 (dd, *J* = 7.5, 12.6 Hz, 1H, 3-CH_2), 2.48 (dd, *J* = 5.2, 12.6 Hz, 1H, 3-CH_2), 3.05 (br s, 1H, NH), 3.64 (br s, 2H, NH_2), 3.73 (m, 2H, CH_2), 3.98 (m, 1H, CH), 6.18 (d, *J* = 2.5 Hz, 1H, 6-H), 6.35 (dd, *J* = 2.5, 8.4 Hz, 1H, 8-H), 6.93 (d, *J* = 8.4 Hz, 1H, 9-H). *Anal.* Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.23; H, 8.32; N, 17.89.

7-Amino-4-methyl-5(2,2,2trifluoroethyl)-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one **(Ie)**

Synthesized from **Ve** [9]. Yellowish crystals (mixture of diethyl ether and hexane, 95% yield), mp 156-158 °C; IR: 3454, 3371, 3174, 1677 cm^{-1}; ^1H NMR: δ 1.08 (d, *J* = 6.1 Hz, 3H, CH_3), 2.22-2.40 (m, 2H, CH_2), 3.3-3.7 (br s, 2H, NH_2), 3.53 (dq, *J* = 8.9, 15.4 Hz, 1H, 5-CH_2), 3.83 (dq, *J* = 8.6, 15.4 Hz, 1H, 5-CH_2), 4.02 (m, 1H, CH), 6.42-6.46 (m, 2H, 6-H, 8-H), 6.81 (m, 1H, 9-H), 7.83 (br s, 1H, NH). *Anal.* Calcd. for $C_{12}H_{14}F_3N_3O$: C, 52.75; H, 5.16; N, 15.38. Found: C, 52.87; H, 5.24; N, 15.30.

4-Methyl-7-nitro-1-propyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one **(Vc)**

To a solution of 2.2 g (10.0 mmol) of 4-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one [10] in 150 ml of benzene, 0.5 g (1.50 mmol) of tetrabutylammonium bromide, 15 ml 50% aqueous sodium hydroxide and 1.8 ml (20.0 mmol) of 1-bromopropane were added. The reaction was performed according to the procedure method A previously described by us [9]. The working-up of the reaction mixture gave 1.6 g (61%) of **Vc**. Yellowish crystals (ethyl acetate), mp 116-118 °C; IR: 3296, 1651, 1517, 1344 cm^{-1}; ^1H NMR: δ 0.85 (t, *J* = 7.4 Hz, 3H, CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, CH_3), 1.54 (m, 2H, CH_2), 2.28 (dd, *J* = 7.4, 12.9 Hz, 1H, 3-CH_2), 2.57 (dd, *J* = 5.2, 12.9 Hz, 1H, 3-CH_2), 3.55 (br s, 1H, NH), 3.86 (m, 2H, CH_2), 4.12 (m, 1H, CH), 7.29 (d, *J* = 8.8 Hz, 1H, 9-H), 7.76 (d, *J* = 2.6 Hz, 1H, 6-H), 7.89 (dd, *J* = 2.5, 8.8 Hz, 1H, 8-H). *Anal.* Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.61; H, 6.63; N, 16.12.

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Regina Janciene, Algirdas Klimavicius, Zita Staniulyte, Stanislava Palaikiene, Jonas Meskauskas, Algirdas Palaima. 1,5-Aizvietotu 7-amino-tetrahidro-1,5-benzodiazepīn-2-onu ciklokondensācija ar α,β-nepiesātinātiem ketoniem.
Modificētas Debnera-Millera reakcijas apstākļos pētīta 7-amino-4-metil-1-R^1-5-R^2-1,3,4,5-tetrahidro-2H-1,5-benzodiazepīn-2-onu (1-R^1 = H, CH_3, C_3H_7; 5-R^2 = H, CH_3, CH_2CF_3) iedarbība ar α,β- nepiesātinātiem ketoniem – dimetil-2-oksoglutakonātu un metil-4-okso-2-pentenoātu. Ciklizācijai izmantots sauss hlorūdeņraža šķīdums ledus etiķskābē. 7-Amino-4-metil-1-R^1-1,3,4,5-tetrahidro-2H-1,5-benzodiazepīn-2-onu (1-R^1 = H, CH_3, C_3H_7 un 5-R^2 = H) kondensācijā ar dimetil-2-oksoglutakonātu sintezēti jaunas kondensētas heterosistēmas četrcikliski savienojumi ar leņķisku uzbūvi – 4,8-diokso-6,7,8,9-tetrahidro-4H-[1,4]diazepīno[3,2,1-hi]pirido[4,3,2-cd]indolo-2-karbonskābes metilesteri **IIa-c**. 7-Amino-4-metil-5-alkil-1,3,4,5-tetrahidro-2H-1,5-benzodiazepīn-2-onu (1-R^1 = H un 5-R^2 = CH_3, CH_2CF_3) reakcijā ar oksoglutakonātu iegūti tricikliski produkti – 2-okso-2,3,4,5-tetrahidro-1H-[1,4]diazepīno[2,3-g]hinolīno-8,10-dikarbonskābes dimetilesteri **IIId,e**. 7-Amino-1,4-dimetil(vai 4,5-dimetil)-1,3,4,5-tetrahidro-2H-1,5-benzodiazepīn-2-onu reakcijā ar metil-4-oksopentenoātu veidojas 2-okso-2,3,4,5-tetrahidro-1H-[1,4]diazepīno[2,3-g]hinolīno-8-karbonskābes 10-metilaizvietoti atvasinājumi **IVb,d**. Šiem savienojumiem ir kondensētas heterosistēmas

lineāra uzbūve, neatkarīgi no izejas savienojumu diazepīna cikla aizvietotājiem 1- un 5- vietās. Pierādīts, ka policiklisko produktu struktūru, t.i., ciklizācijas reakcijas virzienu nosaka izejas amīnu aizvietotāji 1- un 5- vietās un α,β-nepiesātinātā ketona uzbūve.

Регина Янчене, Алгирдас Климавичюс, Зита Станюлите, Станислава Палайкене, Ионас Мяшкаускас, Алгирдас Палайма. Циклоконденсация 1,5-замещенных 7-амино-тетрагидро-1,5-бензодиазепин-2-онов с α,β-непредельными кетонами.

Изучено взаимодействие 7-амино-4-метил-1-R^1-5-R^2-1,3,4,5-тетрагидро-2H-1,5-бензодиазепин-2-онов (1-R^1 = H, CH_3, C_3H_7 и 5-R^2 = H, CH_3, CH_2CF_3) с α,β-непредельными кетонами – диметил-2-оксоглутаконатом и метил-4-оксо-2-пентеноатом в условиях модифицированной реакции Дебнера-Миллера, используя для циклизации раствор сухого хлористого водорода в ледянной уксусной кислоте. Конденсацией 7-амино-4-метил-1-R^1-1,3,4,5-тетрагидро-2H-1,5-бензодиазепин-2-онов (1-R^1 = H, CH_3, C_3H_7 и 5-R^2 = H) с диметил-2-оксоглутаконатом синтезированы четырехциклические производные, новой конденсированной гетеросистемы, имеющей угловое строение, метиловые эфиры 4,8-диоксо-6,7,8,9-тетрагидро-4H-[1,4]диазепино[3,2,1-hi]пиридо[4,3,2-cd]индоло-2-карбоновой кислоты **IIa-c**. При взаимодействии 7-амино-4-метил-5-алкил-1,3,4,5-тетрагидро-2H-1,5-бензодиазепин-2-онов (1-R^1 = H и 5-R^2 = CH_3, CH_2CF_3) с оксоглутаконатом получены трициклические производные, диметиловые эфиры 2-оксо-2,3,4,5-тетрагидро-1H-[1,4]диазепино[2,3-g]хинолино-8,10-дикарбоновой кислоты **IIId,e**. Реакция 7-амино-1,4-диметил(или 4,5-диметил)-1,3,4,5-тетрагидро-2H-1,5-бензодиазепин-2-онов и метил-4-оксо-пентеноата протекает с образованием 10-метилзамещенных производных 2-оксо-2,3,4,5-тетрагидро-1H-[1,4]диазепино[2,3-g]хинолино-8-карбоновой кислоты **IVb,d**, имеющих линейное строение конденсированной гетеросистемы в независимости от заместителей в 1- и 5-положениях диазепинового цикла исходных соединений. Таким образом, установлено, что структура полициклических продуктов, т.е. направление реакции циклизации, определяется присутствием заместителей в 1- и 5-положениях исходных аминов, а так же строением α,β-непредельного кетона.