Chemistry of Heterocyclic Compounds, Vol. 44, No. 6, 2008

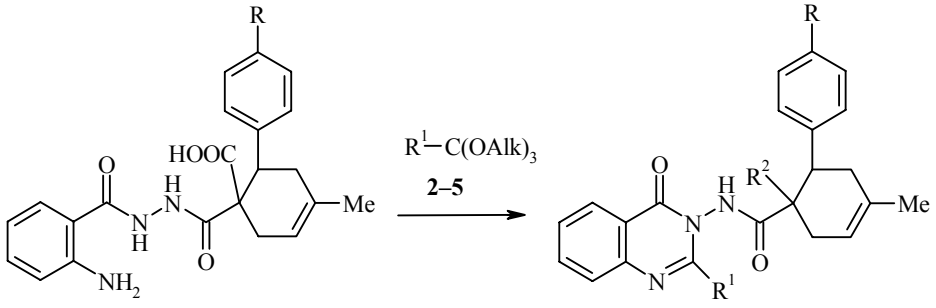
SYNTHESIS AND STEREOCHEMICAL STRUCTURE OF DERIVATIVES OF 2-SUBSTITUTED 3-CYCLO-HEXENYLAMIDOQUINAZOLIN-4-ONES OBTAINED FROM N′-CYCLOHEXENECARBONYL-SUBSTITUTED HYDRAZIDES OF 2-AMINOBENZOIC ACID AND CERTAIN ORTHOESTERS

D. Zicane[1], I. Raviņa[1], Z. Tetere[1], M. Petrova[2], and E. Liepinsh[2]

In the reaction of N′-cyclohexenecarbonyl-substituted hydrazides of 2-aminobenzoic acid with the trialkyl esters of formic, acetic, valeric, and benzoic acids at room temperature 3-cyclohexenyl-amidoquinazolin-4-ones with the respective substituent at the C-2 atom of the quinazoline ring were obtained. The spatial structure of the obtained compounds was studied by homonuclear and heteronuclear NMR.

Keywords: formic, acetic, valeric, benzoic orthoesters, quinazolin-4-ones, N′-cyclohexenecarbonyl-substituted 2-aminobenzohydrazides, two-dimensional NMR spectroscopy, spatial structure.

In a continuation of researches on the synthesis of quinazolinone derivatives [1, 2], among which substances with sedative activity on the central nervous system [3, 4], anticonvulsive activity [5], and antiallergic activity [6] were found, this article sets out the results of investigations into the synthesis of 2-substituted 3-cyclohexenylamidoquinazolinones, which have not been described in the literature, in the reactions of N′-cyclohexenecarbonyl-substituted 2-aminobenzohydrazides **1a,b** with certain orthoesters **2-5**.

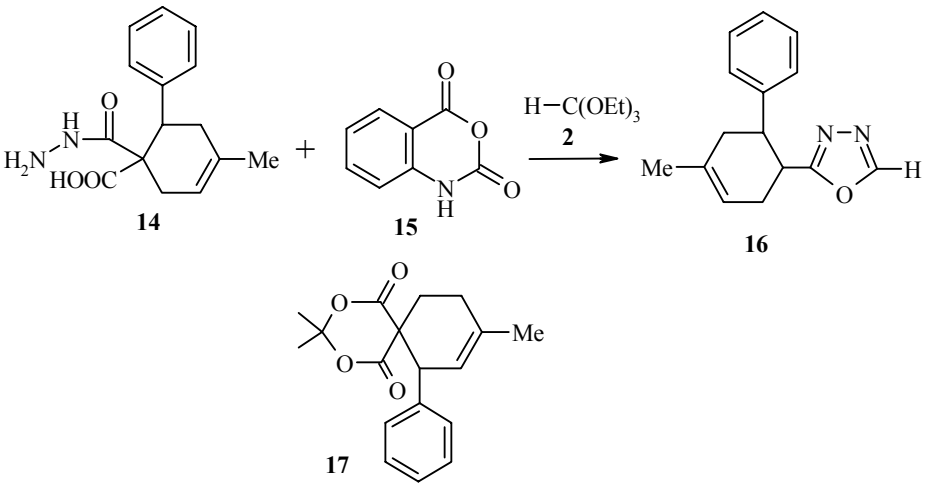


1a,b **6a,b–13a,b**

1, 6–13 a R = H, **b** R = F; **2, 3** Alk = Et, **4, 5** Alk = Me; **2, 6, 10** R^1 = H, **3, 7, 11** R^1 = Me, **4, 8, 12** $R^1 = (CH_2)_3Me$, **5, 9, 13** R^1 = Ph; **6–9** R^2 = COOH, **10–13** R^2 = H

[1]Riga Technical University, Riga LV-1048. Latvia; e-mail: daina_zi@ktf.rtu.lv. [2]Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: marina@osi.lv.Translated form Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 899-906, June, 2008. Original article submitted September 26, 2006.

These reactions are attractive in that the C-2 atom of the quinazoline ring can be modified depending on the structure of the orthoester, and the C-1 atom of the cyclohexene can be modified depending on the reaction conditions.



We established that the N′-cyclohexenecarbonylhydrazides **1a**,**b**, which we synthesized [1] from the monohydrazides of 2-arylcyclohexene-1,1-dicarboxylic acid [7] and isatoic anhydride **15**, react with orthoformic (**2**) and orthoacetic (**3**) triethyl esters and also with orthovaleric (**4**) and orthobenzoic (**5**) methyl esters even at room temperature. The respective 3-cyclohexenylamido-2-R^1-quinazolin-4-ones **6-9** are formed with high yields.

In solvents with a boiling point above 100°C the carboxyl group at the C-1 atom of the cyclohexene ring of the monohydrazides **1a**,**b** is decarboxylated [2]. It was therefore possible to synthesize the quinazolin-4-ones **10-13** by cyclization of the hydrazides **1a**,**b** with the orthoesters **2-5** by heating above 100°C or by cyclization of the synthesized 1-carboxyquinazolinones **6-9** by boiling in DMF. Experimentally, however, we were unable to isolate compounds **10-13** by any of these methods.

TABLE 1. Characteristics of 3-Cyclohexenylamido-2-R^1-quinazolin-4-ones **6-9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
6a	$C_{23}H_{21}N_3O_4$	68.76 / 68.48	5.44 / 5.25	10.18 / 10.42	237-240	74.3
6b	$C_{23}H_{20}FN_3O_4$	64.97 / 65.55	4.81 / 5.02	9.85 / 9.97	229-230.5	96.1
7a	$C_{24}H_{23}N_3O_4$	69.16 / 69.05	5.66 / 5.55	10.35 / 10.07	250-251	75.5
7b	$C_{24}H_{22}FN_3O_4$	67.33 / 67.20	5.11 / 5.09	9.58 / 9.65	240-241	93.8
8a	$C_{27}H_{29}N_3O_4$	70.25 / 70.07	6.37 / 6.36	9.10 / 9.14	229-231	63.1
8b	$C_{27}H_{28}FN_3O_4$	68.10 / 67.90	6.02 / 5.92	3.00 / 2.93	241-242	85.7
9a	$C_{29}H_{25}N_3O_4$	72.60 / 72.64	5.32 / 5.25	8.91 / 8.76	228-230	71.8
9b	$C_{29}H_{24}FN_3O_4$	69.90 / 70.01	4.91 / 4.86	8.39 / 8.45	242-243	90.9

TABLE 2. The H NMR Spectra of the Synthesized Compounds **6-9**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
6a	1.69 (3H, s, CH_3); 2.01-2.90 (4H, m, $2CH_2$); 3.91 (1H, m, H-2); 5.50 (1H, m, H-5); 7.27-8.15 (9H, m, Ar); 11.31 (1H, br. s, COOH); 13.04 (1H, br. s, NH)
6b	1.71 (3H, s, CH_3); 2.23-2.95 (4H, m, $2CH_2$); 3.84 and 3.85 (1H, two m, H-2); 5.51 and 5.55 (1H, two m, H-5); 6.78-8.23 (8H, m, Ar); 11.15 (1H, br. s, COOH); 12.98 (1H br. s, NH)
7a	1.71 (3H, s, CH_3); 2.30 (3H, s, CH_3); 1.97-4.03 (5H, m, $2CH_2$, H-2); 5.50 and 5.55 (1H, two m, H-5); 7.25-8.08 (9H, m, Ar); 11.03 and 11.21 (1H, two br. s, COOH); 13.03 (1H, br. s, NH)
7b	1.72 (3H, s, CH_3); 1.96-2.98 (4H, m, $2CH_2$); 3.89 and 4.03 (1H, two m, H-2); 5.56 (1H, m, H-5); 7.08-8.13 (8H, m, Ar); 11.23 (1H, br. s, COOH); 12.51 (1H, br. s, NH)
8a	0.91 (3H, t, $^3J = 7$, CH_3); 1.35 (2H, m, CH_2); 1.72 (2H, m, CH_2); 1.74 (3H, s, CH_3); 2.05-3.03 (6H, m, $3CH_2$); 3.83 and 3.95 (1H, two m, H-2); 5.51 and 5.55 (1H, two m, H-5); 7.20-8.07 (9H, m, Ar); 10.23 and 11.11 (1H, two br. s, COOH); 13.02 (1H, br. s, NH)
8b	0.94 (3H, t, $^3J = 7$, CH_3); 1.39-3.07 (10H, m, $5CH_2$); 1.72 (3H, s, CH_3); 3.93 and 3.94 (1H, two m, H-2); 5.51 and 5.62 (1H, two c, H-5); 6.69-8.23 (8H, m, Ar); 9.37 and 10.03 (1H, two br. s, COOH); 13.06 (1H, br. s, NH)
9a	1.30 and 1.42 (3H, c, CH_3); 1.50-2.56 (4H, m, $2CH_2$); 3.68(1H, m, H-2); 4.80 and 5.42 (1H, two m, H-5); 7.07-8.14 (14H, m, Ar); 10.96 and 11.17 (1H, two br. s, COOH); 12.85 (1H, br. s, NH)
9b	1.63 and 1.71 (3H, s, CH_3); 1.98-2.86 (4H, m, $2CH_2$); 3.76 (1H, m, H-2); 4.81 and 5.52 (1H, two m, H-5); 6.76-8.24 (13H, m, Ar); 10.85 (1H, br. s, COOH) 12.51 (1H, br. s, NH)

On the basis of one example we checked the possibility of producing the quinazolinone **6a** by direct synthesis from the hydrazide of 2-phenylcyclohexene-1,1-dicarboxylic acid (**14**), isatoic anhydride **15**, and triethyl orthoformate **2** without previous synthesis and isolation of the N′-cyclohexenecarbonyl-substituted hydrazide of aminobenzoic acid **1a**. However, our experiment was unsuccessful in so far as the reaction product was the 2-substituted 1,3,4-oxadiazole **16**, which we had synthesized earlier [9].

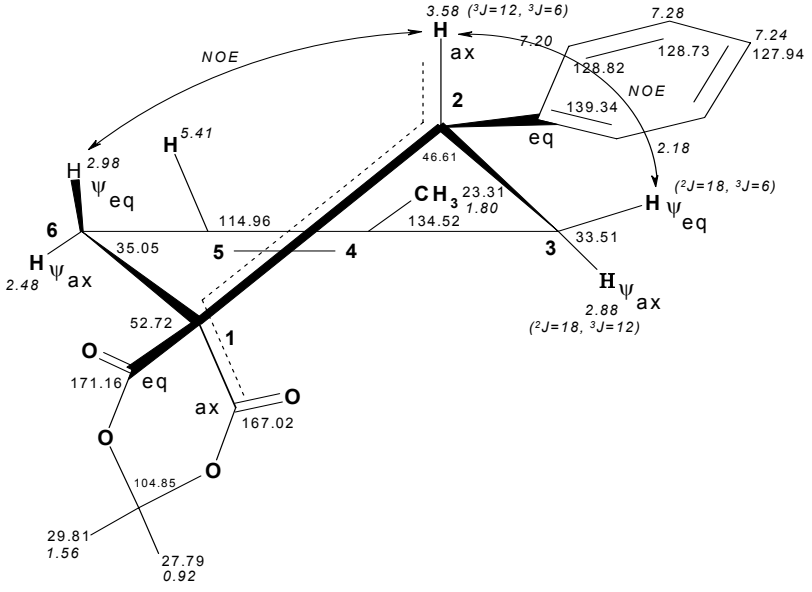


Fig. 1. The three-dimensional structure of the model compound **17**; here and in Fig. 2 δ^1H is in italics and δ^{13}C is in normal type.

The composition of the synthesized products was confirmed by the results from elemental analysis (Table 1) and by the data from the ^{1}H NMR spectra (Table 2), in which the signals for the protons of all fragments of the molecule were observed in their characteristic regions: Multiplets for the magnetically nonequivalent protons of the two methylene groups at positions 3 and 6 of the cyclohexene ring are recorded in the region of 1.7-2.9 ppm, singlets for the 4-Me groups are observed at 1.71-1.76 ppm, and the broad signals for

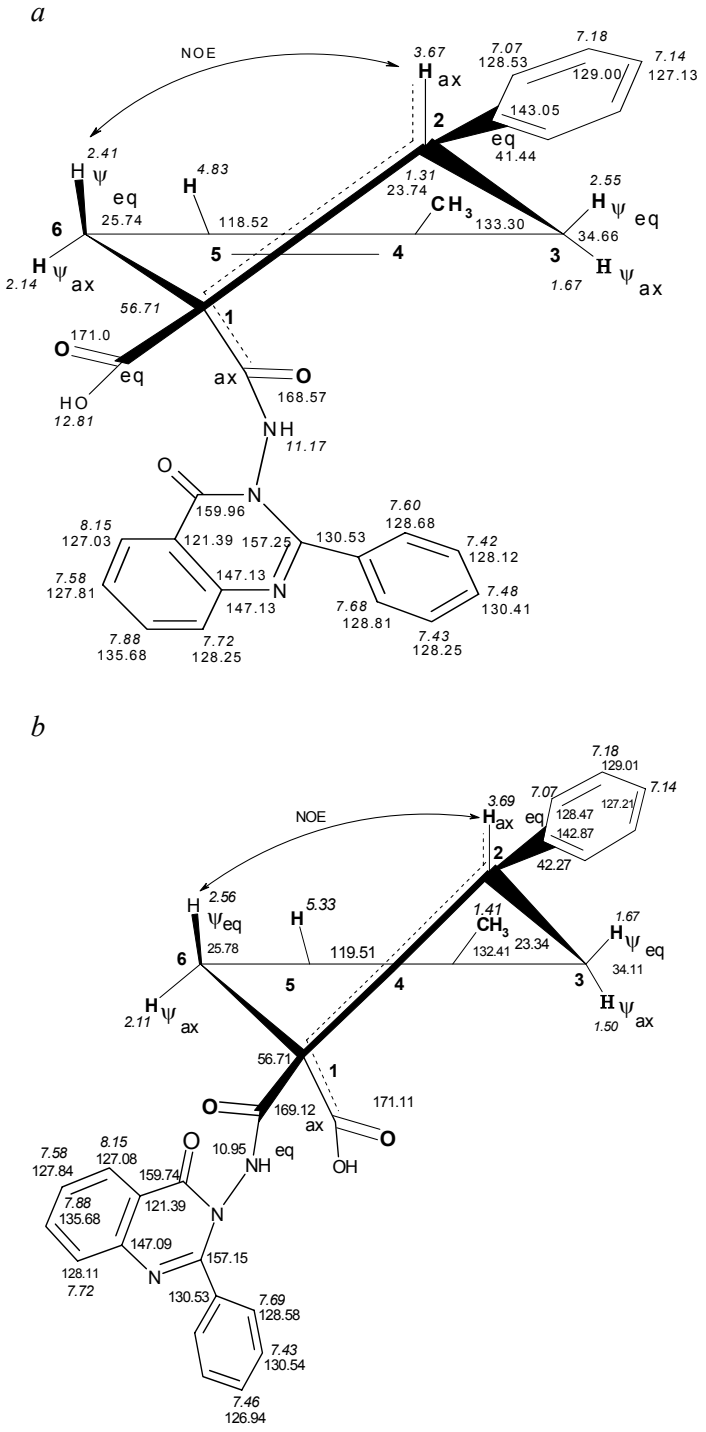


Fig. 2. The three-dimensional structure of the major stereoisomer (*a*) and minor stereoisomer (*b*) of compound **9a**.

the H-5 proton at the double bond resonate in the region of 5.5-5.9 ppm. However, a feature of the ^{1}H NMR spectra of the compounds synthesized was the fact that a double set of resonance signals in a ratio of ~3:2 was observed for some of the protons, but the resolving power of the spectrometer at 200 MHz did not allow more detailed analysis of the remaining signals. However, the one-dimensional ^{1}H and ^{13}C NMR spectra of compound **9a**, recorded on a spectrometer at 600 MHz, contained a double set of all the resonance signals of various intensities, which may indicate two possible configurations for the substituents at position 1 of the cyclohexene ring. In order to check this assumption we established the configuration of the stereoisomers for the case of compound **9a** and also of the model **17** by one- and two-dimensional NMR spectroscopy (1D-NOESY, 2D-NOESY, ^{13}C, ^{13}C–^{1}H HMBC, ^{13}C–^{1}H HSQC, ^{1}H-^{1}H ROESY, ^{1}H–^{1}H TOCSY). Diagrams of the three-dimensional structures of compounds **17** and **9** with the assignment of the chemical shifts are presented in Figs. 1 and 2.

In the NOESY spectra of the compounds (Fig. 3) there are strong cross peaks between the geminal protons H-2 and H-6 and also between the methyl group and the H-5 proton sterically close to them.

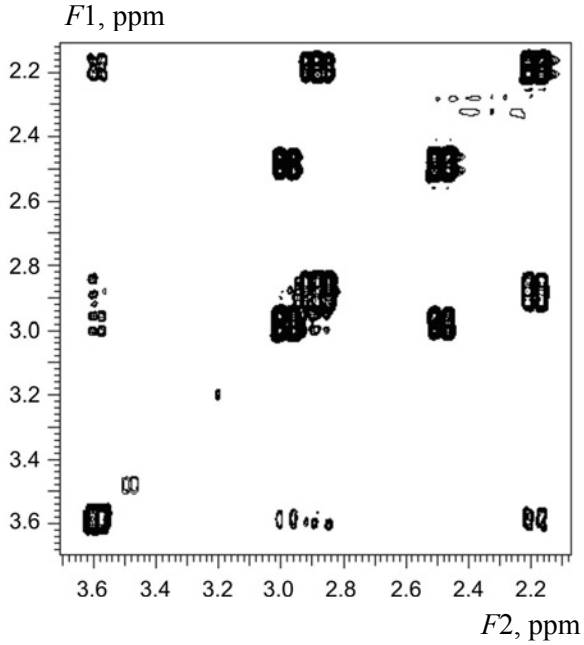


Fig. 3. A fragment of the NOESY spectrum of compound **17**.

This makes it possible to distinguish between the 3- and 6-CH_2 groups, the analysis of which is made difficult by the proximity of the chemical shifts and also by the overlap of their resonance signals with the signals of the solvent. The equatorial orientation of the 2-phenyl substituent is demonstrated by the vicinal constants, the values of which between the axial H-2_{ax} and H-$3_{\psi ax}$ protons amount to 12, and those between H_{ax}-2 and $H_{\psi eq}$-3 amount to 5 Hz (**17**).

The model compound **17** was used for the assignment of the carbonyl carbon atoms in the ^{13}C NMR spectra. It is known that the intensity of the cross peaks in the HMBC spectra is proportional to the vicinal spin–spin coupling constants between the carbon and hydrogen atoms, and here $^{3}J_{trans} > {}^{3}J_{cis}$ [8]. The value of the delay that we used for regeneration of the long-range ^{13}C–^{1}H spin–spin coupling corresponded to 11 Hz. The high intensity of the cross peak of the H_{ax}-2 proton with the carbonyl group (166 ppm) indicates the *trans* orientation in relation to the proton. Consequently, the carbonyl group, which resonates in the downfield region at 171 ppm, has the equatorial orientation in the *half-chair* of cyclohexene **17** (Fig. 4).

Thus, the $^{1}H–^{13}C$ HMBC spectra made it possible to make a stereochemical assignment of these carbonyl groups and then to use this approach for the structural identification of the stereoisomers of compound **9a**, differing in the stereochemical orientation of the carboxyl and amide groups. For compound **9a** the amide carbonyl was identified unambiguously since broad signals for the NH and COOH groups, of which the NH signal of the predominant isomer is easily identified by the cross peak in the $^{1}H–^{13}C$ HMBC spectrum, are observed in the downfield region. In this case the stronger cross peak in the $^{1}H–^{13}C$ spectrum between the H_{ax}-2 proton and the carbon atom of the amide group (168.57 ppm) favors the axial arrangement of this group and, consequently, the equatorial arrangement of the carboxyl group in the compounds (Fig. 5).

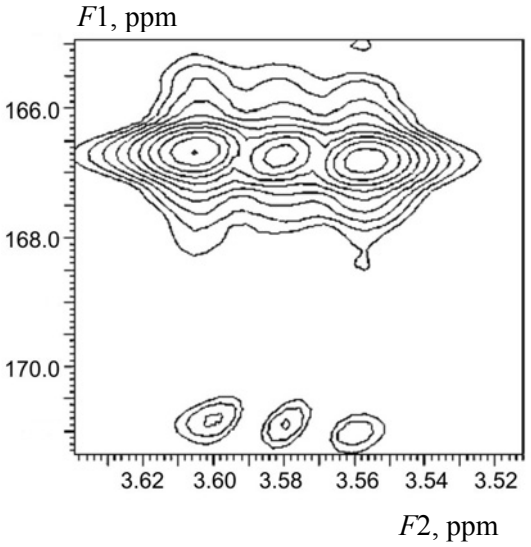


Fig. 4. A fragment of the HMBC spectrum of compound **17**.

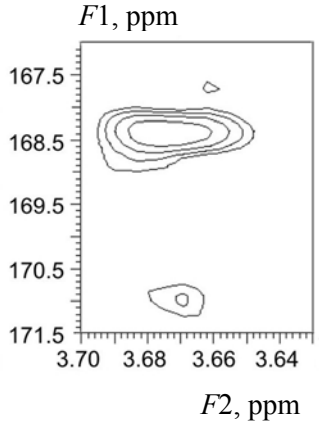


Fig. 5. A fragment of the HMBC spectrum of compound **9a**.

On the basis of the foregoing it can be supposed that the structure of the remaining compounds **6-9** can also be represented as a mixture of two stereoisomers.

EXPERIMENTAL

The ^{1}H NMR spectra of compounds **6-9** were obtained on a Varian-Mercury BB instrument (200 MHz) in DMSO-d_6 with TMS as internal standard. The one-dimensional ^{1}H and two-dimensional $^{1}H–^{1}H$ TOCSY, $^{1}H–^{1}H$ ROESY, and 2D-NOESY spectra and also the ^{13}C, $^{13}C–^{1}H$ HMBC, and $^{13}C–^{1}H$ HSQC spectra of compounds **9a** and **17** were recorded on a Varian-Inova spectrometer (600 MHz) fitted with a cryoscopic sensor in solutions in DMSO (**9a**) and $CDCl_3$ (**17**) at 25°C using the gradient pulse technique. The mixing time in the 2D-ROESY spectrum amounted to 200 (in 2D-NOESY-1c) and 70 msec (in TOCSY). The ^{13}C-HMBC spectra were recorded with an evolution time of 62.5 msec of coupling for the generation of long-range correlations. For all the two-dimensional spectra we used a 4098×1024 matrix table, which ensured τ_{2max} = 250 msec for ^{1}H during recording along the *F*2 axis and τ_{1max} = 100 msec for ^{1}H or τ_{1max} = 50 msec for ^{13}C during recording along the *F*1 axis. In order to improve the signal–noise ratio the matrix table before Fourier transformation was augmented twice with zeros and multiplied by a cosine function. The chemical shifts of the hydrogen and carbon atoms are presented in parts per million with reference to the residual signals of the solvent (2.5 and 39.5 ppm respectively).

The individuality of the synthesized compounds was checked by TLC on Silufol plates in solvent systems: 95:5:3 chloroform–methanol–acetic acid and 100:50:2 benzene–acetone–acetic acid.

3-[1-Hydroxycarbonyl-4-methyl-2-(4-R-phenyl)-4-cyclohexen-1-ylamido]-2-R^1-quinazolin-4-ones 6-9. A suspension of 0.7 mmole of the N′-cyclohexenecarbonyl-containing hydrazides **1a**,**b** in 2 ml of trialkyl orthoformate (**2**), orthoacetate (**3**), orthovalerate (**4**), and orthobenzoate (**5**) (in the last case 2 ml of ethanol was added) was stirred at room temperature. When the hydrazides had dissolved and a precipitate had appeared after 5 min for (**7b**), 10 for (**7a**), 30 for (**8b**), 45 for (**6b**), 60 for (**6a** and **8b**), and 129 min for (**9a** and **9b**) the stirring was continued for a further 3 h. The precipitate was filtered off and washed on the filter with methyl *tert*-butyl ether for (**6a**-**9a**) or hexane for (**6b**-**9b**).

2-(4-Methyl-2-phenyl-4-cyclohexen-1-yl)[1,3,4]oxadiazole (16). A suspension of the monohydrazide of 2-phenylcyclohexene-1,1-dicarboxylic acid (**14**) (0.3 g, 1.0 mmol) [7] and isatoic anhydride (**15**) (0.167 g, 1.0 mmol) in triethyl orthoformate **2** (3 ml) was boiled for 5 h. The excess of the ortho ester was distilled, and the residue was recrystallized from hexane. We obtained 0.12 g (48%) of compound **16**, which according to the analytical and spectral data was similar to the compound obtained in [9] from the anhydride **14** and triethyl orthoformate **2**.

REFERENCES

1. D. Zicāne, I. Raviņa, Z. Tetere, and M. Petrova, *Khim. Geterotsikl. Soedin.*, 894 (2007). [*Chem. Heterocycl. Comp.*, **43**, 755 (2007)].
2. I. Ravina, Z. Tetere, D. Zicane, and M. Petrova, *Latv. J. Chem.,* 263 (2006).
3. S. Hayao, H. Havera, and W. Strycker, *J. Med. Chem.*, **8**, 807 (1965).
4. R. Baronnet, R. Callendret, and L. Blanchard, *Eur. J. Med. Chem.*, **18**, 241 (1983).
5. D. Wenzel, *Arch. J. Pharm.*, **44**, 550 (1955).
6. N. P. Peet, L. E. Baugh, Sh. Sunder, and J. E. Lewis, *J. Med. Chem.*, **29**, 2403 (1986).
7. D. R. Zitsane, I. T. Ravinya, I. A. Riikure, Z. F. Tetere, E. Yu. Gudrinietse, and U. O. Kalei, *Zh. Org. Khim.*, **36**, 521 (2000).
8. J. L. Marshall, *Carbon-Carbon and Carbon-Proton NMR Couplings. Methods in Stereochemical Analysis 2,* Verlag Chemie Intern. (1983), 241 pp.
9. D. Zicane, Z. Tetere, I. Raviņa, and M. Petrova, *Khim. Geterotsikl. Soedin.*, 1065 (2004). [*Chem. Heterocycl. Comp.*, **40**, 916 (2004)].