Chemistry of Heterocyclic Compounds, Vol. 45, No. 8, 2009

ANTHRANOYLHYDRAZONES OF ALIPHATIC ALDEHYDES AND THEIR CYCLIZATION TO QUINAZOLIN-4-ONE DERIVATIVES

A. Yu. Ershov[1]*, N. A. Lovushkina[1], I. V. Lagoda[2], S. I. Yakimovich[3], I. V. Zerova[3], V. V. Pakal'nis[3], and V. V. Shamanin[1]

The isomeric transition of 2-aminobenzoylhydrazones of aliphatic aldehydes 2-$H_2NC_6H_4CONHN=CHAlk$ (Alk = Me, Et, Pr, Bu) in chloroform-d_1 solution into the cyclic 1,2-dihydroquinazolin-4-one form has been studied. The structure of the obtained compounds was demonstrated by methods of ^1H and ^{13}C NMR spectroscopy.

Keywords: 2-aminobenzoylhydrazones, benzo-1,3,4-triazepines, 1,2-dihydroquinazolin-4(3H)-ones, ring-chain tautomerism.

Condensation products of carbonyl compounds with N-methyl-N'-(2-aminobenzoyl)hydrazine and N,N'-dimethyl-N'-(2-aminobenzoyl)hydrazine have a cyclic 1,3,4-triazepine structure [1-6]. On interacting N-acyl-N'-(2-aminobenzoyl)hydrazine with carbonyl compounds derivatives of 1,2-dihydroquinazolin-4-one are formed [7, 8]. The products of reaction of 2-aminobenzoylhydrazine unsubstituted at the hydrazine nitrogen atom were assigned a linear structure [7-11]. The formation of possible cyclic forms as a result of intramolecular attack by the nitrogen atom of the NH_2 group at the C=N bond of the hydrazone fragment was not considered.

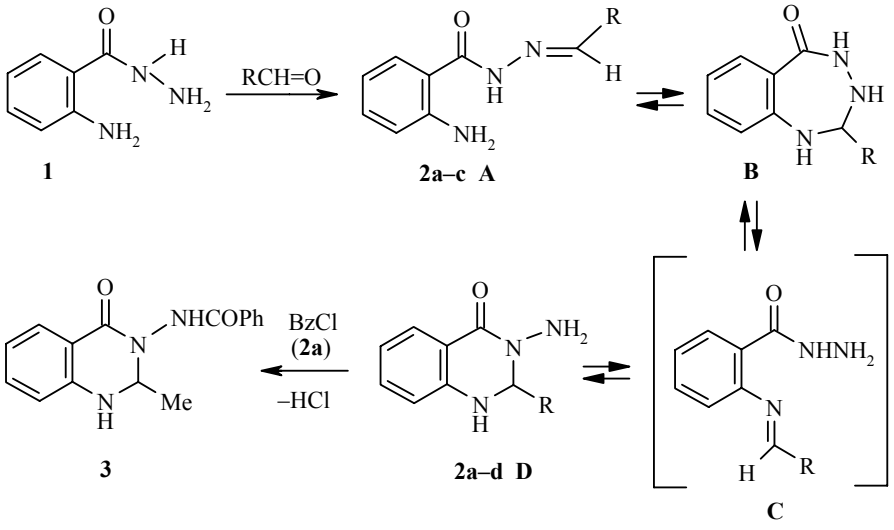
The aim of the present work was to study the structure of 2-aminobenzoylhydrazones of a series of aliphatic aldehydes **2a-d**, and also their inclination towards different variants of cyclization in solution leading to the formation of ring forms.

Compounds **2a-d** were obtained in 55-75% yield after briefly maintaining 2-aminobenzoylhydrazide and the appropriate aldehyde in benzene at 25°C (see Table 1 and Experimental).

* To whom correspondence should be addressed, e-mail: ershov@hq.macro.ru.

[1]Institute of Macromolecular Compounds, Russian Academy of Sciences, Saint Petersburg 199004, Russia.
[2]Scientific Research Test Center (Medical and Biological Protection) of the State Research Test Institute of Military Medicine, Defence Ministry of Russian Federation, Saint Petersburg 195043, Russia; e-mail: lagodai@peterst ar.ru.
[3]Saint Petersburg State University, Saint Petersburg 198504, Russia; e-mail: viktoriapakalnis@mail.ru.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1214-1219, August, 2009. Original article submitted October 17, 2008.



a R = Me, **b** R = Et, **c** R = Pr, **d** R = Bu

Judging by the change in ^{1}H NMR spectra with time, compounds **2a-c** in the crystalline state were found to be in the linear hydrazone form **A**. In the ^{1}H NMR spectra of compounds **2a-c** taken directly after solution in $CDCl_3$ one set of resonance signals was observed corresponding to this form. In this a low field signal shows the azomethine proton of appropriate multiplicity at 7.5 ppm (Table 2). In the ^{13}C NMR spectra signals at 150 and 160 ppm, characteristic of carbon atoms at C=N and C=O bonds respectively (Table 3), correspond to the linear form **A**. The position of these signals enables a conclusion to be made between the possible *E,E′*- and *E,Z′*-conformational isomers of the linear form **A** in favor of the *E,Z′*-isomer. It is known that analogous signals of the *E,E′*-conformer for acylhydrazones of aldehydes lie at 145 and 170 ppm respectively [12, 13]. The existence of *E,Z*-configurational isomerism relative to the C=N bond was not considered by us, since aldoacylhydrazones exist predominantly in the *E*-configuration relative to this bond [12-15].

Several hours after dissolving compounds **2a-c** in $CDCl_3$ signals appeared in the ^{1}H NMR spectra corresponding to the cyclic 1,3,4-triazepine form **B**. Typical features of this form, the content of which did not exceed 10% for the compounds investigated, are a low-field signal for the NH group proton at 9.0 ppm and a signal of appropriate multiplicity at 5.0 ppm (H-2) (Table 2). In the ^{13}C NMR spectra the signal of the sp^3-hybrid atom at 70 (C-2) and the signal at 170 ppm (C-5) (Table 3) correspond to the triazepine form **B**.

TABLE 1. Physicochemical Characteristics of Compounds **2a-d**

Compound	Form	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
2a	**A**	$C_9H_{11}N_3O$	60.93 / 61.00	6.30 / 6.26	23.64 / 23.71	149-151 (150 [9])	55
	D	$C_9H_{11}N_3O$	61.07 / 61.00	6.22 / 6.26	23.78 / 23.71	Oil	98
2b	**A**	$C_{10}H_{13}N_3O$	62.78 / 62.81	6.79 / 6.85	22.06 / 21.97	140-143	75
	D	$C_{10}H_{13}N_3O$	62.87 / 62.81	6.91 / 6.85	21.89 / 21.97	Oil	98
2c	**A**	$C_{11}H_{15}N_3O$	64.42 / 64.37	7.31 / 7.37	20.54 / 20.47	83-85	60
	D	$C_{11}H_{15}N_3O$	64.31 / 64.37	7.44 / 7.37	20.56 / 20.47	Oil	99
2d	**D**	$C_{12}H_{17}N_3O$	65.80 / 65.73	7.75 / 7.81	19.21 / 19.16	Oil	65

TABLE 2. ^{1}H NMR Spectra of Compounds **2a-d**

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)*
2a	**A** (93%): 2.03 (3H, d, *J* = 5.4, CH_3); 5.44 (2H, br. s, NH_2); 6.58-7.36 (4H, m, Ar); 7.53 (1H, q, *J* = 5.4, HC=N); 9.34 (1H, br. s, NHCO) **B** (7%): 1.35 (3H, d, *J* = 5.1, CH_3); 4.51 (2H, br. s, 2NH); 5.18 (1H, q, *J* = 5.1, H-2); 8.96 (1H, br. s, NHCO) **D**: 1.41 (3H, d, *J* = 6.2, CH_3); 4.27 (2H, br. s, NH_2); 4.38 (1H, br. s, NH); 4.92 (1H, q, *J* = 6.2, H-2); 6.52-7.76 (4H, m, Ar)
2b	**A** (95%): 1.73 (3H, t, *J* = 5.4, CH_3); 2.40 (2H, m, CH_2); 5.45 (2H, br. s, NH_2); 6.58-7.35 (4H, m, Ar); 7. 47 (1H, t, *J* = 5.0, HC=N); 9.06 (1H, br. s, NH) **B** (5%): 0.93 (3H, t, *J* = 7.5, CH_3); 2.26 (2H, m, CH_2); 4.47 (2H, br. s, 2NH); 4.94 (1H, t, *J* = 5.3, H-2); 8.90 (1H, br. s, NHCO) **D**: 0.95 (3H, t, *J* = 7.5, CH_3); 1.88 (2H, m, CH_2); 4.42 (2H, br. s, NH_2); 4.48 (1H, br. s, NH); 4.79 (1H, t, *J* = 5.5, H-2); 6.62-7.85 (4H, m, Ar)
2c	**A** (92%): 0.91 (3H, t, *J* = 7.2, CH_3); 1.50 (2H, m, CH_2); 2.27 (2H, m, CH_2); 5.42 (2H, br. s, NH_2); 6.56-7.39 (4H, m, Ar); 7. 50 (1H, t, *J* = 4.8, HC=N); 9.64 (1H, br. s, NH) **B** (8%): 0.88 (3H, t, *J* = 7.2, CH_3); 1.57 (2H, m, CH_2); 2.18 (2H, m, CH_2); 4.35 (2H, br. s, 2NH); 4.97 (1H, t, *J* = 5.4, H-2); 9.01 (1H, br. s, NHCO) **D**: 0.89 (3H, t, *J* = 7.3, CH_3); 1.33 (2H, m, CH_2); 1.76 (2H, m, CH_2); 4.27 (2H, br. s, NH_2); 4.38 (1H, br. s, NH); 4.92 (1H, q, *J* = 6.4, H-2); 6.52-7.76 (4H, m, Ar)
2d	**D**: 0.88 (3H, t, *J* = 7.2, CH_3); 1.29 (4H, m, $2CH_2$); 1.82 (2H, m, CH_2); 4.32 (2H, br. s, NH_2); 4.53 (1H, br. s, NH); 4.80 (1H, t, *J* = 5.4, H-2); 6.51-7.82 (4H, m, Ar)

*The spectrum of form **A** was taken 2 h after dissolving, and of form **D** 7 days after dissolving.

TABLE 3. ^{13}C NMR Spectra of Compounds **2a-d**

Compound	Form	Chemical shifts, δ, ppm*			
		C=N or C-2	C=O	CH_3	CH_2
2a	**A**	152.1	165.4	20.1	
	D	69.2	164.1	19.7	
2b	**A**	150.5	165.8	10.6	26.7
	D	73.9	163.8	8.7	25.5
2c	**A**	151.8	165.6	13.5	19.8, 34.5
	B	71.9	170.1	13.5	19.2, 35.1
	D	72.6	163.6	13.5	17.6, 34.1
2d	**D**	72.8	163.6	13.7	22.2, 26.4, 32.1

*Signals of C arom. lie in the range 114.4-145.3 ppm.

Seven days after dissolving compounds **2a-c** in $CDCl_3$ the shape of the ^1H NMR spectra had undergone significant changes. The proportions of linear form **A** and triazepine form **B** were significantly reduced, and an additional set of resonance signals appeared in the spectra, belonging to a second cyclic form. Two broadened singlet signal for the NH group protons located close to one another at 4.40-4.50 ppm, and a signal of appropriate multiplicity at 4.80 ppm in the ^1H NMR spectrum correspond to this form. The appearance of the indicated signals is impossible to link with any conformational process of the triazepine form **B**, since the signal of the amide H-4 proton at 9.00 ppm characteristic of the triazepine ring is absent from the ^1H NMR spectra of compounds **2a-c** for the second cyclic form. The observed phenomenon may only be linked with the appearance in solution of the 1,2-dihydroquinazoline form **D**, the formation of which is the result of opening the triazepine ring accompanied by cleavage of the C–N(3) bond and a repeat attack by the nitrogen atom of the hydrazide group at the C=N bond of the alkylidenimine fragment of the intermediate linear form **C**.

Later, 14 days after solution in $CDCl_3$, judging by the spectral data, the quinazoline form **D** remains the only form in solutions of compounds **2a-c** and it may be isolated in the pure state by removing the solvent (see Experimental). In other words, we have discovered and confirmed spectrally the recyclization of 2-amino-benzoylhydrazone **A** → 1,2-dihydroquinazolin-4(3H)-one **D** proceeding with time.

For the condensation product of 2-aminobenzoic acid hydrazide with valeraldehyde **2d** the process of conversion into dihydroquinazoline begins directly after mixing the starting materials and is complete after several hours. Consequently to isolate in the crystalline state or confirm spectrally trace amounts of linear hydrazone **A** or the cyclic 1,3,4-triazepine **B** form were unsuccessful.

Additional confirmation of the 1,2-dihydroquinazoline structure **D** of compounds **2a-d** is their modification in N-benzoylation reactions (see Experimental). Compound **3**, the product of reacting 2-methyl-1,2-dihydroquinazolin-4(3H)-one **2a** with benzoyl chloride, proved to be identical in its physicochemical and spectral characteristics with that obtained by an alternative route, *viz*. by the interaction of N-benzoyl-N'-(2-aminobenzoyl)hydrazine with acetaldehyde [8].

The final condensation products of aliphatic aldehydes with 2-aminobenzoylhydrazide therefore do not have a linear 2-aminobenzoylhydrazone structure but a cyclic 1,2-dihydroquinazoline structure. It is interesting to compare the structure of the condensation products of aliphatic aldehydes with aroylhydrazines containing functional substituents (OH, SH, or NH_2) in position 2 of the aromatic nucleus. Salicyloylhydrazones of aldehydes are completely in the linear hydrazone form [16, 17], and the condensation products of aldehydes with 2-mercaptobenzoic acid hydrazide have predominantly the cyclic 1,3,4-triazepine structure [12, 18]. In the case of condensation products of aldehydes with 2-aminobenzoylhydrazide, the 2-aminobenzoylhydrazone formed in the initial step in the course of time undergoes a cascade of conversions of the "ring opening – ring closing" type, leading to the formation of 1,2-dihydroquinazoline derivatives in the concluding step of the process.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were obtained on a Bruker AV-400 spectrometer (400 and 100 MHz respectively) in $CDCl_3$, internal standard was TMS. The quantitative composition of the tautomeric forms was determined by integration of the respective signals in the ^1H NMR spectra. Error of measurements was ±1%. A check on the progress of reactions and the purity of the obtained compounds was effected by TLC on Silufol UV-254 plates in the system benzene–acetone, 4:1.

2-Aminobenzoylhydrazones of Aldehydes 2a-c (Form A). A mixture of 2-aminobenzoic acid hydrazide **1** (1.51 g, 10 mmol) and the appropriate aldehyde (15 mmol) in benzene (50 ml) was maintained at 25°C for 2 h. The mixture was dried over Na_2SO_4, the solvent removed, and petroleum ether (50 ml) added to

the residue. The precipitated crystals were filtered off, washed with hexane, and dried. Under analogous conditions the condensation of hydrazide **1** with valeraldehyde leads to the formation of 2-butyl-1,2-dihydroquinazolin-4(3H)-one **2d**.

2-Alkyl-1,2-dihydroquinazolin-4(3H)-ones 2a-c (Form D). The appropriate 2-aminobenzoylhydrazone **2a-c** (5 mmol) in chloroform (10 ml) was maintained for 14 days. The solvent was removed, and the 1,2-di-hydroquinazoline isolated as a viscous oily liquid in quantitative yield.

3-Benzoylamino-2-methyl-1,2-dihydroquinazolin-4(3H)-one (3). Benzoyl chloride (0.7 g, 50 mmol) was added to a solution of 2-methyl-1,2-dihydroquinazolin-4(3H)-one **2a** (0.85 g, 50 mmol) in chloroform (10 ml) and triethylamine (0.75 ml) with cooling to 0°C. The mixture was maintained at 25°C for 2 h, washed with water, the organic layer was dried over Na_2SO_4, filtered, the solvent was removed, and the residue crystallized by adding petroleum ether. The precipitated crystals were filtered off, washed with hexane, dried, and recrystallized from a mixture of water–ethanol, 4:1. Yield was 55%; mp 184-186°C (lit. mp 189-190°C [8]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (3H, d, *J* = 5.6, CH_3); 5.21 (1H, q, *J* = 5.6, H-2); 5.61 (1H, br. s, NH); 6.62-7.82 (9H, m, Ar); 10.23 (1H, br. s, NHCO). ^{13}C NMR spectrum, δ, ppm: 19.0 (CH_3); 68.1 (C-2); 114.9-146.7 (Ar); 163.8 (C-4); 166.2 (C=O). Found, %: C 68.27; H 5.43; N 14.86. $C_{16}H_{15}N_3O_2$. Calculated, %: C 68.31; H 5.37; N 14.94.

REFERENCES

1. K. Pihlaja, M. F. Simeonov, and F. Fülöp, *J. Org. Chem.,* **62**, 5080 (1907).
2. F. Fülöp, M. F. Simeonov, and K. Pihlaja, *Tetrahedron*, 48, 531 (1992).
3. R. E. Valters, F. Fülöp, and D. Karbonits, *Adv. Heterocycl. Chem.*, **64**, 251 (1995).
4. O. Hromatka, M. Knollmüller, and F. Krenmüller, *Monatsh. Chem.*, **100**, 941 (1968).
5. L. Lázár and F. Fülöp, *Eur. J. Org. Chem.*, **16**, 3025 (2003).
6. M. Gál, E. Tihanyi, and P. Dvortsák, *Acta Chim. Acad. Sci, Hung.*, **123**, 55 (1986).
7. P. S. N. Reddy and P. P. Reddy, *Indian J. Chem.*, **27B**, 135 (1988).
8. G. A. Smirnov, E. P. Sizova, O. A. Lukyanov, I. V. Fedyanin, and M. Yu. Antipin, *Izv. Akad. Nauk, Ser. Khim.*, 2311 (2003).
9. G. Heller, *J. Prakt. Chem.*, **131**, 82 (1931).
10. K. Neuvonen, F. Fülöp, H. Neuvonen, M. Simeonov, and K. Pihlaja*, J. Phys. Org. Chem.*, **10**, 55 (1997).
11. P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 1242 (1957).
12. A. Yu. Ershov, I. V. Lagoda, M. V. Mokeev, S. I. Yakimovich, I. V. Zerova, V. V. Pakal'nis, and V. V. Shamanin, *Khim. Geterotsikl. Soedin.*, 460 (2008). [*Chem. Heterocycl. Comp.*, **44**, 356 (2008)].
13. K. N. Zelenin, S. V. Oleinik, V. V. Alekseev, and A. A. Potekhin, *Zh. Obshch. Khim.*, **71**, 1116 (2001).
14. Yu. P. Kitaev and B. I. Buzykin, *Hydrazones* [in Russian], Nauka, Moscow (1974), p. 381.
15. N. A. Parpiev, V. G. Yusupov, S. I. Yakimovich, and Kh. T. Sharipov, *Acylhydrazones and Their Complexes with Transition Metals* [in Russian], Fen, Tashkent (1988), 164 pp.
16. A. V. Dolgarev, V. V. Lukachina, and O. I. Karpova, *Zh. Anal. Khim.*, **29**, 721 (1974).
17. S. A. Flegontov, Z. S. Titova, A. P. Stolyarov, B. I. Buzykin, and Yu. P. Kitaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1014 (1979).
18. A. Yu. Ershov, I. V. Lagoda, S. I. Yakimovich, V. V. Pakal'nis, and V. V. Shamanin, *Zh. Org. Khim.*, **43**, 1742 (2007).