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SYNTHESIS OF 4- AND 5-SUBSTITUTED 2-METHYL- AND 2-(2-CARBOXYETHYL)-1,2,4-TRIAZINO-[2,3-*a*]BENZIMIDAZOL-4(5)H-3-ONES

T. A. Kuz'menko, V. V. Kuz'menko, A. S. Morkovnik, and L. N. Divaeva

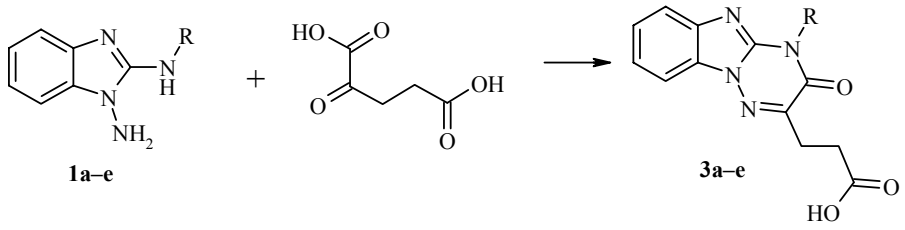
Condensation of 2-alkylamino-1-aminobenzimidazoles and quaternary 1,2-diamino-3R-benzimidazolium salts with pyruvate and α-ketoglutaric acid has given 4- and 5-substituted 2-methyl- and 2-(2-carboxyethyl)-1,2,4-triazino[2,3-a]benzimidazol-4(5)H-3-ones.

Keywords: 1,2-diaminobenzimidazoles, 1,2,4-triazino[2,3-*a*]benzimidazol-4(5)H-3-ones, condensation.

The condensation reaction of 1,2-diaminobenzimidazole with α-keto acids leading to NH-unsubstituted 1,2,4-triazino[2,3-*a*]benzimidazol-4(5)H-3-ones has been studied for pyruvate, 3-benzoylpropan-2-oic acids, and ethylcarboxyformimidate [1-3]. It has been shown before that 2-alkylamino-1-aminobenzimidazoles **1** also cyclize with ethyl pyruvate to the $N_{(4)}$-alkyl-2-methyl derivative of this heterocyclic system [4] which has proved to affect gastric secretion [5].

With the aim of developing methods for the synthesis of novel $N_{(4)}$- and up to this time unreported $N_{(5)}$-substituted 1,2,4-triazino[2,3-*a*]benzimidazol-4(5)H-3-ones we have now studied the reaction of the diamines **1** and quaternary 1,2-diamino-3R-benzimidazolium salts **2** with ethyl pyruvate and α-ketoglutaric acid. This keto acid has attracted out attention in connection with the recent appearance of evidence for multipharmacological activity in carboxy derivatives of isomeric 1,2,4-triazino[4,3-*a*]benzimidazol-3H-4-ones [6,7].

We have shown that refluxing the 2-alkylamino-1-aminobenzimidazoles **1** with α-ketoglutaric acid in glacial acetic acid caused ready cyclization to 4-alkyl-2-(2-carboxyethyl)triazino[2,3-*c*]benzimidazol-5H-3-ones **3a-e** (Tables 1 and 2).



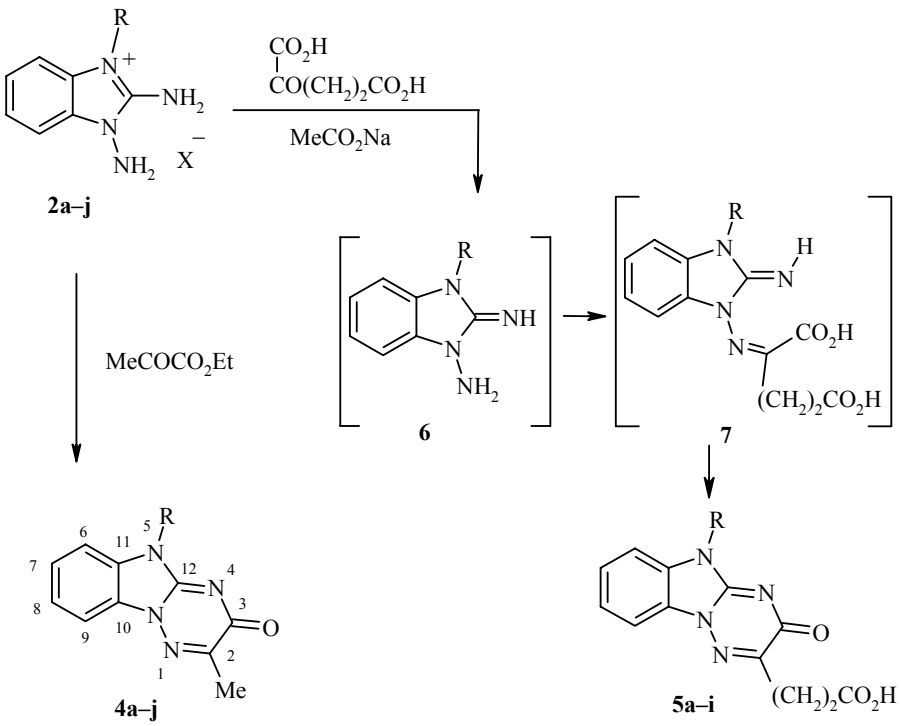
1a–e **3a–e**

1, 3 a R = Me; **b** R = Bn; **c** R = CH_2CH_2OH; **d** R = $CH_2CH_2NEt_2$; **e** R = Ph

Physical and Organic Chemistry Science Research Institute, Rostov State University, Rostov-on-Don 344090, Russia; e-mail: asmork2@ipoc.rsu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 738-747, May, 2006. Original article submitted October 18, 2004.

Even the 2-phenylaminobenzimidazole **1e** [8], in which the nucleophilicity of the secondary amino group is significantly less, is converted to the 4-phenyltriazinone **3e** in 75-80% yield. Cyclization of the 2-(2-hydroxyethyl) derivative **1c** is accompanied by an unwanted O-acetylation which introduces the need to carry out hydrolysis of the ester **3** formed (R = CH_2CH_2OCOMe) by heating in 20% HCl. Hence it was more convenient to use DMF as solvent in the preparation of compound **3c** even though the yield of the reaction product did not exceed 60%. The carboxylic acids **3a-e** are poorly soluble in water but give water soluble salts in dilute base and concentrated NH_4OH solutions. The IR spectra show three extremely characteristic and strong absorption bands for the 4-substituted 2-methyltriazino[2,3-*a*]benzimidazol-3-ones [4] at about 1600, 1620, and 1680 cm^{-1} corresponding to the stretching vibrations of the ring C=C, C=N, and C=O bonds. The ν_{CO} band for the COOH group appears at 1720-1730 cm^{-1}. The ^1H NMR spectra of compound **3** are shown in Table 2 and are in complete agreement with the structure proposed by us.

As has been shown in our study, the quaternary 1,2-diamino-3-R-benzimidazole salts **2** also cyclize with ethyl pyruvate and α-ketoglutaric acid to form the corresponding $N_{(5)}$-R-triazinobenzimidazoles **4** and **5**.



2, **4**, **5 a** R = Me, **b** R = Bz, **c** R = CH_2COMe, **d** R = CH_2CO-Bu-*t*, **e** R = CH_2CO_2Et,
f R = CH_2CH_2OH, **g** R = CH_2CH_2OPh, **h** R = β-piperidinoethyl, **i** R = β-morpholinoethyl;
2, **4 j** R = $CH_2CH_2NEt_2$; **2 a** X = I; **b**, **c**, **e**, **f**, **h**-**j** X = Cl; **d**, **g** X = Br

This reaction is of significant preparative interest since the starting salts **2**, including those with functional substituents, are quite readily formed from 1,2-diaminobenzimidazole and the corresponding alkylating agents [9-11]. In addition, even alkylation of the cyclic NH-unsubstituted 2-methyl-1,2,4-triazino-[2,3-*a*]benzimidazol-4(5)H-3-one compound **4** occurs although in very low yield (the results of these investigations will be published by us later).

The cyclization of salts **2** with α-ketoglutaric acid in refluxing acetic acid occurs with markedly greater difficulty than ethyl pyruvate but, in the presence of sodium acetate or with the introduction of the known imine **6** [10], the yield of the corresponding 2-carboxyethyl derivatives **5** are increased to 75-80%. The role of the

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
3a	$C_{13}H_{12}N_4O_3$	57.62 / 57.35	4.83 / 4.44	20.87 / 20.58	271-272 (DMF)	85
3b	$C_{19}H_{16}N_4O_3$	65.23 / 65.51	4.85 / 4.63	16.43 / 16.08	283-285 (DMF)	82
3c	$C_{14}H_{14}N_4O_4$	55.36 / 55.63	4.86 / 4.67	18.39 / 18.53	258-260 (DMF)	60
3d	$C_{18}H_{23}N_5O_3$	60.22 / 60.49	6.21 / 6.49	20.00 / 19.59	201-202 (DMF)	80
3e	$C_{18}H_{14}N_4O_3$	65.02 / 64.67	4.05 / 4.22	16.67 / 16.76	279-280 (DMF)	78
4a	$C_{11}H_{10}N_4O$	61.45 / 61.67	4.59 / 4.71	26.35 / 26.15	266-267 (EtOH)	73
4b	$C_{17}H_{14}N_4O$	70.55 / 70.33	5.09 / 4.86	9.13 / 9.30	242-243 (BuOH)	78
4c	$C_{13}H_{12}N_4O_2$	61.23 / 60.93	5.04 / 4.72	21.54 / 21.86	261-262 (BuOH)	76
4d	$C_{16}H_{18}N_4O_2$	64.10 / 64.41	6.19 / 6.08	19.13 / 18.78	234-235 (EtOH)	81
4e	$C_{14}H_{14}N_4O_3$	58.92 / 58.74	4.69 / 4.93	19.83 / 19.57	217-218 (EtOH)	74
4f	$C_{12}H_{12}N_4O_2$	59.44 / 59.01	5.16 / 4.95	22.79 / 22.94	250-251 (H_2O)	65
4g	$C_{18}H_{16}N_4O_2$	67.09 / 67.49	5.16 / 5.03	17.81 / 17.49	189-190 (MeCN)	85
4h	$C_{17}H_{21}N_5O$	65.58 / 65.57	6.99 / 6.80	22.53 / 22.49	205-206 (MeCN)	72
4i	$C_{16}H_{19}N_5O_2$	61.33 / 61.33	6.23 / 6.11	22.48 / 22.35	228-229 (PhH)	73
4j	$C_{16}H_{21}N_5O$	63.78 / 64.19	7.02 / 7.07	23.69 / 23.39	117-118 (MeCN)	70
4k	$C_{12}H_{10}N_4O_3$	55.38 / 55.81	3.99 / 3.90	21.94 / 21.70	299-301 (BuOH)	95
5a	$C_{13}H_{12}N_4O_3$	57.00 / 57.35	4.84 / 4.44	20.32 / 20.58	260-262	75
5b	$C_{19}H_{16}N_4O_3$	65.45 / 65.51	4.89 / 4.63	16.18 / 16.08	248-250	80
5c	$C_{15}H_{14}N_4O_4$	57.47 / 57.32	4.33 / 4.49	17.95 / 17.83	224-225	77
5d	$C_{18}H_{20}N_4O_4$	60.27 / 60.67	5.71 / 5.66	15.98 / 15.72	227-228	82
5e	$C_{16}H_{16}N_4O_5$	56.24 / 55.81	5.00 / 4.68	16.20 / 16.27	205-207	75
5f	$C_{14}H_{14}N_4O_4$	55.19 / 55.63	4.78 / 4.67	18.57 / 18.53	242-243	70
5g	$C_{20}H_{18}N_4O_4$	63.28 / 63.49	4.77 / 4.79	15.07 / 14.81	218-220	83
5h	$C_{19}H_{23}N_5O_3$	61.77 / 61.77	6.22 / 6.28	19.21 / 18.96	215-216	68
5i	$C_{18}H_{21}N_5O_4$	58.39 / 58.21	5.44 / 5.70	18.25 / 18.86	253-254	71
5j	$C_{14}H_{12}N_4O_5$	53.00 / 53.17	3.97 / 3.82	17.45 / 17.71	294-295	96

* Compounds **5a-j** were purified by precipitation from aqueous solution.

TABLE 2. ^{1}H NMR Spectra of Compounds **3a-e, 4a-k, 5a-j**

Com-pound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*
1	2
3a	2.70 (2H, t, *J* = 7.2, CH_2); 2.96 (2H, t, *J* = 7.2, CH_2); 3.53 (3H, s, CH_3); 7.21-7.29 (2H, m, H-7,8); 7.60-7.71 (2H, m, H-6,9); 12.33 (1H, br. s, CO_2H)
3b	2.75 (2H, t, *J* = 7.2, CH_2); 3.03 (2H, t, *J* = 7.2, CH_2); 5.36 (2H, s, N–CH_2); 7.29-7.39 (5H, m, H-7,8, *m*- and *p*-H_{Ar}); 7.48-7.52 (2H, m, *o*-H_{Ar}); 7.64-7.68 (1H, m, H-6); 7.71-7.76 (1H, m, H-9); 12.36 (1H, br. s, CO_2H)
3c	2.69 (2H, t, *J* = 7.1, C–CH_2); 2.92 (2H, t, *J* = 7.1, C–CH_2); 3.75 (2H, t, *J* = 5.3, N–CH_2); 4.21 (2H, t, *J* = 5.3, O–CH_2); 7.34-7.46 (2H, m, H-7,8); 7.65-7.72 (2H, m, H-6,9); 12.23 (1H, br. s, CO_2H)
3d	0.90 (6H, t, *J* = 7.0, $(CH_3)_2$); 2.51 (4H, q, *J* = 7.0, $(\underline{CH_2}CH_3)_2$); 2.72 (2H, t, *J* = 7.3, C–CH_2); 2.79 (2H, t, *J* = 7.3, Et_2N–$\underline{CH_2}$); 2.98 (2H, t, *J* = 6.9, C–CH_2); 4.19 (2H, t, *J* = 6.9, $N_{(4)}$–CH_2); 7.27-7.37 (2H, m, H-7,8); 7.61-7.72 (2H, m, H-6,9)
3e	2.75 (2H, t, *J* = 7.0, CH_2); 3.04 (2H, t, *J* = 7.0, CH_2); 7.21-7.36 (2H, m, H-7,8); 7.40-7.61 (6H, m, H_{Ar} and H-6); 7.63-7.78 (1H, m, H-9); 12.16 (1H, br. s, CO_2H)
4a	2.46 (3H, s, CH_3); 3.72 (3H, s, N–CH_3); 7.32-7.46 (3H, m, H-6,7,8); 7.74-7.78 (1H, m, H-9)
4b	2.49 (3H, s, CH_3); 5.39 (2H, s, CH_2); 7.23-7.41 (8H, m, Ar, H-6,7,8); 7.73-7.80 (1H, m, H-9)*[2]
4c	2.31 (3H, s, $COCH_3$); 2.47 (3H, s, CH_3); 5.00 (2H, s, CH_2); 7.09-7.18 (1H, m, H-6); 7.34-7.44 (2H, m, H-7,8); 7.74-7.82 (1H, m, H-9)
4d	1.32 [9H, s, $C(CH_3)_3$]; 2,48 (3H, s, CH_3); 5.18 (2H, s, CH_2); 6.98–7.05 (1H, m, H-6); 7.30-7.40 (2H, m, H-7,8); 7.72-7.80 (1H, m, H-9)
4e	1.22 (3H, s, $CH_2\underline{CH_3}$); 2.31 (3H, s, CH_3); 4.18 (2H, q, $\underline{CH_2}CH_3$); 5.11 (2H, s, CH_2CO); 7.38-7.49 (2H, m, H-7,8); 7.70-7.75 (1H, m, H-6); 7.78–7.82 (1H, m, H-9)
4f	2.29 (3H, s, CH_3); 3.76 (2H, q, *J* = 5.3, OCH_2); 4.21 (2H, t, *J* = 5.3, N–CH_2); 4.92 (1H, s, *J* = 5.4, OH); 7.34-7.46 (2H, m, H-7,8); 7.69 (1H, d, *J* = 7.9, H-6); 7.75 (1H, d, *J* = 7.3, H-9)
4g	2.50 (3H, s, CH_3); 4.37 (2H, t, *J* = 4.9, CH_2); 4.62 (2H, t, *J* = 4.9, CH_2); 6.77 (2H, d, *J* = 8.3, *o*-H_{Ar}); 6.92 (1H, tt, J_1 = 7.3, J_2 = 1.2, *p*-H_{Ar}); 7.18–7.25 (2H, *m*-H_{Ar}); 7.40 (1H, td, J_1 = 7.7, J_2 = 1.3, H-7 or H-8); 7.46 (1H, td, J_1 = 7.8, J_2 = 1.4, H-8 or H-7); 7.64 (1H, dm, *J* = 7.9, H-6), 7.77 (1H, dm, *J* = 7.7, H-9)
4h	1.31-1.64 (6H, m, β- and γ-$CH_{2\ piperidyl}$); 2.33-2.60 (7H, m, CH_3 + α-$CH_{piperidyl}$); 2.71 (2H, t, *J* = 6.0, 5-$CH_2\underline{CH_2}$); 4.31 (2H, *J* = 6.0, t, CH_2-5-$\underline{CH_2}CH_2$); 7.33-7.50 (3H, m, H-6,7,8); 7.76 (1H, d, *J* = 8.5, H-9)
4i	2.30 (3H, s, CH_3); 2.41-2.50 (4H, m, CH_2NCH_2); 2.70 (2H, t, *J* = 6.5, 5-$NCH_2\underline{CH_2}$); 4.29 (2H, t, *J* = 6.5, 5-$\underline{CH_2}CH_2$); 7.38 (1H, td, J_1 = 7.6, J_2 = 1.2, H-7 or H-8); 7.44 (1H, td, J_1 = 7.7, J_2 = 1.3, H-8 or H-7); 7.72 (1H, d, *J* = 7.6, H-6); 7.76 (1H, d, *J* = 7.6, H-9)
4j	0.86 (6H, t, *J* = 7.5, $(\underline{CH_3})_2$); 2.30 (3H, s, CH_3); 2.52 (4H, q, *J* = 7.5, $(\underline{CH_2}CH_3)_2$); 2.81 (2H, t, *J* = 7.0, $\underline{CH_2}NEt_2$); 4.25 (2H, t, *J* = 7.0, 5-NCH_2); 7.28-7.41 (3H, m, H-6,7,8); 7.73-7.80 (1H, d, *J* = 7.5, H-9)
4k	2.30 (3H, s, CH_3); 4.99 (2H, s, CH_2); 7.37-7.48 (2H, m, H-7,8), 7.70 (1H, dd, J_1 = 8.5, J_2 = 1.4, H-6); 7.75 (1H, dd, J_1 = 7.2, J_2 = 1.3, H-9)
5a	2.70 (2H, t, *J* = 7.9, CH_2); 2.94 (2H, t, *J* = 7.9, CH_2); 3.67 (3H, s, CH_3); 7.32-7.46 (2H, m, H-7,8); 7.60 (1H, d, *J* = 8.4, H-6); 7.71 (1H, d, *J* = 7.6, H-9), 12.03 (1H, br. s, CO_2H)
5b	2.69 (2H, t, *J* = 8.5, CH_2); 2.96 (2H, t, *J* = 8.5, CH_2); 5.40 (2H, s, N–CH_2); 7.20-7.46 (7H, m, H_{Ar} and H-7,8); 7.50–7.58 (1H, m, H-6); 7.67-7.76 (1H, m, H-9); 12.04 (1H, br. s, CO_2H)
5c	2.31 (3H, s, CH_3); 2.68 (2H, t, *J* = 7.8, $\underline{CH_2}CH_2COOH$); 2.94 (2H, t, *J* = 7.8, $\underline{CH_2}COOH$); 5.21 (2H, s, CH_2CO); 7.32-7.42 (2H, m, H-7,8); 7.50-7.59 (1H, m, H-6); 7.70-7.79 (1H, m, H-9); 12.02 (1H, br. s, CO_2H)
5d	1.32 (9H, s, $C(CH_3)_3$); 2.65 (2H, t, *J* = 7.8, $\underline{CH_2}CH_2COOH$); 2.97 (2H, t, *J* = 7.8, $\underline{CH_2}CH_2CO_2H$); 5.38 (2H, s, $\underline{CH_2}CO$); 7.38-7.45 (2H, m, H-7,8); 7.50-7.57 (1H, m, H-6); 7.77-7.82 (1H, m, H-9); 12.08 (1H, s, CO_2H)
5e	1.26 (3H, t, *J* = 6.7, CH_3); 2.68 (2H, t, *J* = 5.7, $\underline{CH_2}CH_2CO_2H$); 2.98 (2H, t, $\underline{CH_2}CO_2H$); 4.22 (2H, q, $\underline{CH_2}CH_3$); 5.09 (2H, s, N–CH_2), 7.35-7.44 (2H, m, H-7,8); 7.61-7.70 (1H, m, H-6); 7.71-7.80 (1H, m, H-9); 12.10 (1H, br. s, CO_2H)

TABLE 2 (continued)

1	2
5f	2.68 (2H, t, *J* = 7.3, $\underline{CH_2}CH_2CO_2H$); 2.93 (2H, t, *J* = 7.3, $\underline{CH_2}CO_2H$); 3.76 (2H, t, *J* = 5.6, $\underline{CH_2}OH$); 4.22 (2H, t, *J* = 5.6, N–CH_2); 4.88 (1H, br. s, OH); 7.35-7.44 (2H, m, H-7,8); 7.65-7.74 (2H, m, H-6,9); 12.12 (1H, br. s, CO_2H)
5g	2.66 (2H, t, *J* = 7.2, $\underline{CH_2}CH_2CO_2H$); 2.95 (2H, t, *J* = 7.2, $\underline{CH_2}CO_2H$); 4.36 (2H, t, *J* = 5.0, CH_2); 4.59 (2H, t, *J* = 5.0, CH_2); 6.79 (2H, d, *J* = 7.9, *o*-H_{Ar}); 6.84 (1H, t, *J* = 7.6, *p*-H_{Ar}); 7.17 (2H, t, *J* = 7.9, *m*-H_{Ar}); 7.33-7.46 (2H, m, H-7,8); 7.68-7.76 (2H, m, H-6,9); 12.03 (1H, br. s, CO_2H)
5h	1.30-1.52 (6H, m, β- and γ-$H_{piperidyl}$); 2.35-2.44 (4H, m, α-$H_{piperidyl}$; 2.60-2.80 (4H, m, $\underline{CH_2}CH_2COOH$ and 5-$CH_2\underline{CH_2}$); 2.98 (2H, t, *J* = 7.4, $\underline{CH_2}COOH$); 4.28 (2H, t, *J* = 5.8, 5-$\underline{CH_2}CH_2$); 7.30-7.40 (2H, m, H-7,8); 7.52-7.61 (1H, m, H-6); 7.62-7.71 (1H, m, H-9); 11.90 (1H, br. s, CO_2H)
5i	2.45 (4H, br. t, *J* = 4.5, CH_2NCH_2); 2.62-2.72 (4H, m, $\underline{CH_2}CH_2CO_2H$ and 5-$CH_2\underline{CH_2}$); 2.96 (2H, t, *J* = 7.5, $\underline{CH_2}CO_2H$); 3.43 (4H, br. t, *J* = 4.5, CH_2OCH_2); 4.26 (2H, t, *J* = 7.5, 5-$\underline{CH_2}CH_2$); 7.38-7.48 (2H, m, H-7,8); 7.73 (2H, d, *J* = 8.2, H-6,9); 12.20 (1H, br. s, CO_2H)
5j	2.70 (2H, t, *J* = 7.1, $\underline{CH_2}CH_2COOH$); 2.93 (2H, t, *J* = 7.1, $\underline{CH_2}CO_2H$); 5.00 (2H, s, 5-CH_2); 7.39-7.50 (2H, m, H-7,8); 7.70-7.79 (2H, m, H-6,9); 12.25 (1H, br. s, CO_2H)

* Solvents DMSO-d_6 for compounds **3a-e, 4d-f,i,k, 5a-j** or $CDCl_3$ for **4a-c,g,h,j**.

*[2] ^{1}H NMR spectrum, DMSO-d_6, δ, ppm: 2.31 (3H, s, CH_3); 5.39 (2H, s, CH_2); 7.23-7.45 (7H, m, Ar + H-7,8); 7.54-7.62 (1H, m, H-6); 7.74-7.81 (1H, m, H-9).

sodium acetate, in this case, includes preliminary activation of both nucleophilic centers of the salts **2** *via* their conversion to the reactive compounds **6** which enables both a readier formation of the intermediate ketimines **7** and their subsequent closure to the triazinones **5**.

It is interesting to note that the 3-acetonyl- and 3-pivaloylmethyl-1,2-diaminobenzimidazolium salts **2c,d**, which might undergo intramolecular condensation with the actual C=O group to the known 9-aminoimidazo[1,2-*a*]benzimidazoles [10], give exclusively the 5-acetonyl(pivaloylmethyl)triazino-benzimidazoles **4c,d**, **5c,d**.

Similarly to the reaction involving the diamine **1c**, the cyclization process of the 3-(2-hydroxyethyl)-substituted salt **2f** occurs with acetylation of the OH group but the formed acetoxy derivatives **4, 5** (R = CH_2CH_2OCOMe) are readily hydrolyzed by boiling 20% HCl to the triazinones **4f, 5f**. Acid hydrolysis of the esters **4e, 5e** gave the acetic acid derivatives **4k, 5j** (R = CH_2CO_2H).

A comparative analysis of the parameters for the isomeric molecules which might serve in structural investigations shows that, when compared with their $N_{(4)}$-isomers, the $N_{(5)}$-triazinobenzimidazoles **4** generally have a higher melting point with lower solubility in low polarity organic solvents and show markedly lower chromatographic mobility. The IR spectra of the $N_{(5)}$-substituted compounds **4,5** shown a ring carbonyl absorption shifted to 1630-1640 cm^{-1} with low intensity while the acid carbonyl stretching vibration is at 1700-1705 cm^{-1}.

In the ^{1}H NMR spectra of the 5-alkyl-substituted triazinones **4a,b,h,j** in $CDCl_3$ the H-9 proton multiplet appears at lowest field (7.7-7.9 ppm) and the general multiplet for the H-6,7,8 protons is found at 7.2-7.5 ppm. The correctness of the assignment for the H-6 and H-9 protons was made by chemical shift calculation for the protons in the model molecule 2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-one using the GIAO (RHF/6-31G//RHF/6-31G) method. In spite of the fact that the calculation systematically increases δ by 0.2-0.6 ppm the predicted chemical shift of the H-9 proton is to low field of the H-6 proton by 0.71 ppm and this is quite close the actually observed values.

In the spectrum of the 5-(2-phenoxyethyl) derivative **4g** the H-6 proton signal is shifted to low field to 7.64 ppm, separated into other multiplet. The deshielding of the H-6 proton in this case evidently occurs as a result of the steric effect of the oxygen atom of the substituent in the conformation having a *gauche* configuration for the dimethylene fragment (in which the RHF/6-31G calculated distance between the H-6 and O atoms is minimised at 3.10 Å (Fig. 1).

The spectra of the 5-acetonyl- and 5-pivaloylmethyl derivatives **4c,d** show an H-6 signal which is conversely shifted relative to the H-7 and H-8 multiplet to high field to 7.08-7.10 ppm. The difference in chemical shifts of the H-6 and H-9 protons, each of which can appear as a doublet of multiplets, increases to about 0.7 ppm.

According to our analysis of the possible conformations of compound **4c** such a somewhat unexpected shielding effect of the N-acetylmethyl substituents is most likely a result of the predominance of those conformations in which the alkyl groups are twisted to the H-6 proton side. The shielding of this proton simultaneously hinders the deshielding effect of the carbonyl group.

It was interesting that changing from $CDCl_3$ to DMSO-d_6 led to a marked shift of the H-6 proton signal of the $N_{(5)}$-substituted compounds **4** to low field by about 0.4-0.6 ppm to 7.7-7.8 ppm when compared with their $N_{(4)}$-isomers. This is evidently due to the formation of complexes between the polar compounds **4** and the solvent (cf. [9]). Calculated data for the model bimolecular system 5-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-one with DMSO using the RHF/6-31G** method confirmed the possible formation of such a complex

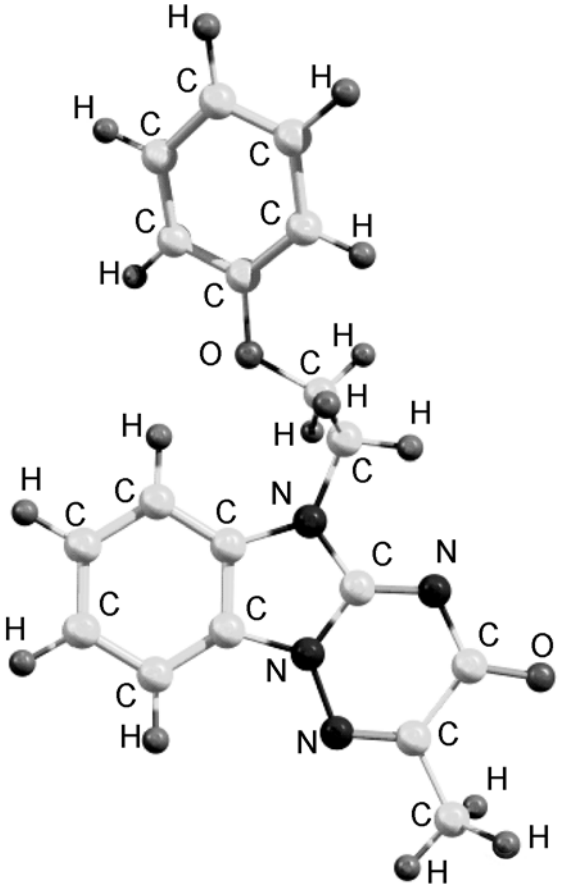


Fig. 1. 5-(2-Phenoxyethyl)-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-one (**4g**).
Conformation with a *gauche* configuration of the dimethylene bridge.

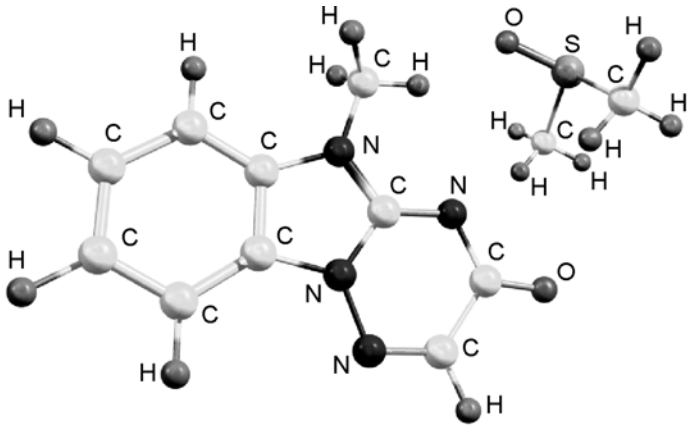


Fig. 2. Structure of the complex of 5-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-one with DMSO calculated using the Hartree–Fock method.

having a negative energy of stabilization of 8.2 kcal/mol and a plane of symmetry coinciding with the plane of the heterocyclic system. The S=O fragment of the DMSO molecule is placed in the heterocyclic plane on the $N_{(5)}$–$C_{(11)}$–$N_{(4)}$–$C_{(3)}$–O polarized atom chain side and oriented with the oxygen atom towards to N–Me group and the S–Me groups found over and under the plane of the hetero ring (Fig. 2).

Judging from the values of the internuclear distances the complex discussed is partially stabilized by three weak nonclassical hydrogen bonds of the type C–H···O and C–H···N with the participation of one of the protons of the N-methyl group and two protons of the S-methyl groups. The nitrogen atom in position 4 and the oxygen atom of DMSO serve as proton acceptors. The calculated hydrogen bonds lengths S=O···H–CH_2–N and the two virtually equivalent N(4)···H–CH_2–S bonds are respectively 2.30, 2.81, and 2.82 Å. In the complex of 5-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-one with DMSO a further energetic minimum is revealed with a greater energy about 2 kcal/mol and with localization of the DMSO molecule over the plane of the heterocyclic system.

EXPERIMENTAL

IR spectra were recorded using vaseline oil on a Specord IR-75 instrument. The ^{1}H NMR spectra were recorded on a Unity-300 (300 MHz) instrument. Monitoring of the reaction course and the purity of the compounds obtained was carried out by TLC on activity grade III Al_2O_3 plates using chloroform eluent and iodine vapor for visualization. Quantum-chemical calculations were performed using the PC GAMESS (6.4)* version and the original GAMESS (US) [12] program package. The geometry of the calculated structure was initially optimized using the semiempirical PM3 method. Estimation of the stabilization energy of the 5-methyl-1,2,4-triazino[2,1-*a*]benzimidazol-4H-3-one–DMSO complex was carried out with null point energy vibrational correction.

1,2-Diamino-3-(2-hydroxyethyl)benzimidazolium Chloride (2f). A solution of 1,2-diamino-benzimidazole [9] (1.48 g, 0.01 mol) and ethylenechlorohydrin (0.7 ml, 0.01 mol) in DMF (6 ml) was refluxed for 30 min. The precipitate which separated on cooling was filtered and washed with acetone to give 1.9 g (83%) of colorless crystals; mp 252-253°C (DMF). Found, %: C 47.02; H 5.93; Cl 15.07; N 24.84. $C_9H_{13}ClN_4O$. Calculated, %: C 47.27; H 5.73; Cl 15.50; N 24.50.

* Alex Granovsky, http://www.classic.chem.msu.su/gran/gamess/index.html.

1,2-Diamino-3-(2-phenoxyethyl)benzimidazolium Bromide (2g) was prepared similarly to salt **2f** in 74% yield as colorless crystals; mp 264-265°C (DMF). Found, %: C 51.22; H 5.11; Br 23.23; N 5.73. $C_{15}H_{17}BrN_4O$. Calculated, %: C 51.59; H 4.91; Br 22.88; N 6.04.

1,2-Diamino-3-(2-piperidinoethyl)benzimidazolium Chloride (2h). A solution of 1,2-diamino-benzimidazole (1.48 g, 0.01 mol) and 2-piperidinoethyl chloride (1.8 g, 0.012 mol) in alcohol (15 ml) was refluxed for 1.5 h. The precipitate (0.2 g) of side product (dispiro-N,N'-dipiperidinopiperazinium dichloride) was filtered off from the hot solution. The filtrate was evaporated to half volume and the precipitate formed on cooling was filtered off to give 2.15 g (72%) of salt **2h** as colorless crystals; mp 238-239°C (alcohol). Found, %: C 56.80; H 7.44; Cl 11.65; N 23.16. $C_{14}H_{22}ClN_5$. Calculated, %: C 56.84; H 7.50; Cl 11.98; N 23.67.

1,2-Diamino-3-(2-morpholinoethyl)benzimidazolium Chloride (2i) was prepared similarly to **2h** in 90% yield as colorless crystals; mp 257-258°C (alcohol). Found, %: C 52.02; H 7.07; Cl 11.99; N 23.61; $C_{13}H_{20}ClN_5O$. Calculated, %: C 52.43; H 6.77; Cl 11.91; N 23.52.

1,2-Diamino-3-(2-diethylaminoethyl)benzimidazolium Chloride (2j) was prepared in the same way as **2h** but the product was precipitated from the alcohol solution with ether. Yield 67% as colorless crystals; mp 223-225°C (2-propanol). Found, %: C 55.00; H 7.95; Cl 13.02; N 25.07. $C_{13}H_{22}ClN_5$. Calculated, %: C 55.02; H 7.81; Cl 12.49; N 24.68.

4-Substituted 2-(2-Carboxyethyl)-1,2,4-triazino[2,3-*a*]benzimidazol-5H-3-ones (3a-e). Solutions of the 2-alkylamino-1-aminobenzimidazoles **2a,b,d,e** [4, 9] (5 mmol) and α-ketoglutaric acid (0.73 g, 5 mmol) in glacial acetic acid (8 ml) were refluxed for 30 min. The precipitate separated on cooling was filtered off, washed with water, and recrystallized.

Compound 3c was prepared similarly in DMF.

5-Substituted 2-Methyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-ones (4a-j). A suspension of 5 mmol of the quaternary salt **2** (synthesis of compounds **2a,b** reported in [9], salts **2c,d** in [10], and salt **2e** in [11]) and ethyl pyruvate (0.6 ml, 5 mmol) in glacial acetic acid (30 ml) was refluxed for 1.5-2 h to complete solution of the precipitate and then for a further 30 min. The solvent was removed in vacuo and the residue was treated with water. The precipitate formed was filtered off and purified chromatographically on an Al_2O_3 column (2 × 10 cm) using chloroform as eluent (R_f 0.35).

5-Substituted 2-(2-Carboxyethyl)-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-ones (5a-i). A suspension of the quaternary salt **2** (5 mmol) and α-ketoglutaric acid (0.73 g, 5 mmol) in glacial acetic acid (30-40 ml) was refluxed in the presence of anhydrous sodium acetate (1.26 g, 15 mmol) for 2-2.5 h to complete solution of the precipitate and then for a further 1 h. The solvent was evaporated to half volume and the precipitate formed was filtered off and washed with water.

2-Methyl- and 2-(2-Carboxyethyl)-5-carboxymethyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-ones (4k, 5j). Solutions of the esters **4e, 5e** (3 mmol) in conc. HCl (5 ml) were refluxed for 20 min. The precipitate formed upon cooling was filtered off and washed with water.

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