Reactions of N'-acyl- and N'-tosyl-substituted hydrazides of 2-aminobenzoic acid with carbonyl compounds

G. A. Smirnov,^a* E. P. Sizova,^a O. A. Luk 'yanov,^a I. V. Fedyanin,^b and M. Y. Antipin^b

 ^aN. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: smir@ioc.ac.ru
^bA. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5085

The reactions of N'-acyl and N'-tosyl-substituted hydrazides of 2-aminobenzoic acid with aliphatic, aromatic, and heterocyclic aldehydes or aliphatic ketones afforded 3-acyl- and 3-tosylamido-1,2-dihydroquinazolin-4-one derivatives, respectively. The structures of the reaction products were established by NMR spectroscopy and X-ray diffraction analysis.

Key words: N'-acyl- and N'-tosylhydrazides of 2-aminobenzoic acid, aldehydes, ketones, reactions; 2-substituted 3-acylamido-1,2-dihydroquinazolin-4-ones and 3-tosylamido-1,2-dihydroquinazolin-4-ones; nuclear Overhauser effect, X-ray diffraction analysis.

1,2-Dihydroquinazolin-4-one (DHQ) derivatives exert targeted action on the central nervous system by exhibiting anticonvulsive¹ and sedative^{2,3} activities. To search for DHQ possessing potential biological activities, we synthesized DHQ containing amide substituents at the N(3) atom. Data on procedures for the preparation of compounds of this type are scarce in the literature. The reactions of 2-aminobenzoic acid hydrazides (ABAH) containing acyl substituents at the N' atom with carbonyl compounds would be expected to open the simplest route to these compounds. This is supported by the reaction of an N'-ethoxycarbonyl derivative of ABAH with aldehyde to give 3-ethoxycarbonylamido-1,2-dihydroquinazolin-4-one, which has been described earlier.⁴ However, the structure of the latter reaction product has not been unambiguously proved in the cited study.⁴ The structures of Schiff's bases,^{5–7} seven-membered triazepine rings,^{5,6,8} DHQ,^{5,7} and even three-membered aziridine rings⁹ were assigned to the products of reactions of N'-unsubstituted ABAH with carbonyl derivatives.

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In the present study, we examined the reactions of N'-acyl- and N'-tosyl-substituted hydrazides of 2-aminobenzoic acid with carbonyl compounds.

The starting N'-derivatives of ABAH 2a-f were synthesized according to Scheme 1. Compounds 2a-e were prepared by the addition of acetic, benzoic, 4-bromobenzoic, and 4-nitrobenzoic acid hydrazides¹⁰ or monohydrazide of ethyl carbonate (1a-e) to isatoic anhydride. N'-Tosylhydrazide (2f) was synthesized by tosylation of ABAH.¹¹



 $\begin{array}{l} {\sf R} = {\sf Ac} \; ({\bm a}), \; {\sf Bz} \; ({\bm b}), \; 4\text{-}{\sf BrC}_6{\sf H}_4{\sf CO} \; ({\bm c}), \; 4\text{-}{\sf O}_2{\sf NC}_6{\sf H}_4{\sf CO} \; ({\bm d}), \; {\sf EtO}_2{\sf C} \; ({\bm e}), \\ {\sf Ts} \; ({\bm f}) \end{array}$

The reactions of hydrazides 1a-d with isatoic anhydride were carried out in refluxing acetic acid. The reaction of hydrazide 1e was performed in anhydrous ethanol (to prevent hydrolysis of the ester group). The low yields of compounds 2a,b (57–59%) are attributable to subsequent reactions attendant on this synthesis. For instance, it was found that compound 2c underwent intramolecular transformation into 2-(4-bromophenyl)-3,4-dihydro-1,3,4-benzotriazepin-5-one (3) (Scheme 2) (examples of such transformations were published in the literature¹²).

Aldehydes, such as formaldehyde, acetaldehyde, thiophene-2-carbaldehyde, and 2,4-dichlorobenzaldehyde, and ketones, such as acetone and cyclohexanone,

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Scheme 3





 $\begin{array}{l} {{\mathsf{R}}^{1}}={{\text{Ac}}\left({\bm{a}} \right),{{\text{Bz}}\left({\bm{b}} \right),{\text{4-Br}}{{\mathsf{C}}_{6}}{{\mathsf{H}}_{4}}{{\text{CO}}\left({\bm{c}} \right),{\text{4-O}}_{2}}{{\mathsf{NC}}_{6}}{{\mathsf{H}}_{4}}\left({\bm{d}} \right),{\text{EtO}}_{2}{{\text{C}}\left({\bm{e}} \right),} \\ {{\text{Ts}}\left({\bm{f}} \right)} \end{array}$

were used as carbonyl compounds. The principal physicochemical characteristics of the compounds thus synthesized are given in Tables 1-3.

It was found that the reactions of hydrazides 2a-f with carbonyl compounds in EtOH have a general char-



Table 1. Melting points, yields, and elemental analysis data for 1,2-dihydroquinazolin-4(3H)-one derivatives 4–9

Com- pound	m.p./°C	Yield (%)		<u>Found</u> Calcula		Molecular formula	
			С	Н	Х	Ν	
4 a	205-207	49	<u>58.51</u> 58.52	<u>5.62</u> 5.40	_	$\frac{20.40}{20.48}$	$C_{10}H_{11}N_3O_2$
4b	241-244	27	<u>67.20</u> 67.40	$\frac{4.83}{4.90}$	_	<u>15.56</u> 15.72	$C_{15}H_{13}N_3O_2$
4c	254-256	30	<u>51.71</u> 52.04	<u>3.55</u> 3.49	Br, <u>22.76</u> 23.08	<u>12.14</u> 12.14	$C_{15}H_{12}BrN_3O_2$
4d	259-262	31	<u>57.54</u> 57.69	<u>3.85</u> 3.87	_	<u>17.58</u> 17.94	$C_{15}H_{12}N_4O_4$
4 e	151—154	52	<u>56.25</u> 56.16	<u>5.10</u> 4.97	_	<u>15.73</u> 15.96	$C_{11}H_{13}N_3O_3$
4f	213-216	30	<u>56.78</u> 56.74	<u>5.00</u> 4.76	S, <u>9.58</u> 10.09	<u>13.13</u> 13.23	$C_{15}H_{15}N_3O_3S$
5a	169—171	82	<u>59.74</u> 59.99	<u>6.64</u> 6.41	_	<u>19.01</u> 19.08	$C_{11}H_{14}N_3O_2$
5b	189—190	82	<u>67.85</u> 68.31	<u>5.65</u> 5.37	_	<u>15.16</u> 14.94	$C_{16}H_{15}N_3O_2$
5c	197—199	90	<u>53.01</u> 53.35	<u>3.94</u> 3.92	Br, <u>21.78</u> 22.18	<u>11.19</u> 11.66	$C_{16}H_{14}BrN_3O_2$
5d	242—244	83	<u>58.55</u> 58.89	$\frac{4.27}{4.32}$	_	<u>17.17</u> 17.17	$C_{16}H_{14}N_4O_4$
5e	147—150	85	<u>57.84</u> 57.82	<u>6.15</u> 6.07	—	<u>16.69</u> 16.86	$C_{12}H_{15}N_3O_3$
5f	220-222	70	<u>57.70</u> 57.99	<u>5.14</u> 5.17	S, <u>9.46</u> 9.67	<u>12.54</u> 12.68	$C_{16}H_{17}N_3O_3S$

(to be continued)

Table 1	(continued)
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Com- pound	m.p./°C	YieldFound Calculated(%)Calculated				Molecular formula	
			С	Н	Х	Ν	
6a	252—254	75	$\frac{58.48}{58.52}$	<u>4.47</u> 4.56	S, <u>10.90</u> 11.16	<u>14.73</u> 14.62	$C_{14}H_{13}N_3O_2S$
6b	215-216	75	<u>65.50</u> 65.31	<u>4.31</u> 4.33	S, <u>9.24</u> 9.18	<u>11.95</u> 12.03	$C_{19}H_{15}N_3O_2S$
6c	237—239	78	<u>53.02</u> 53.28	<u>3.41</u> 3.29	Br, <u>18.23</u> 18.66	<u>9.93</u> 9.81	$C_{19}H_{14}BrN_3O_2S$
6d	247—249	85	<u>57.69</u> 57.86	<u>3.54</u> 3.58	S, <u>8.41</u> 8.13	<u>14.30</u> 14.21	$C_{19}H_{14}N_4O_4S$
6e	213-216	72	<u>56.64</u> 56.77	<u>4.76</u> 4.76	S, <u>10.54</u> 10.10	<u>13.05</u> 13.24	$C_{15}H_{15}N_3O_3S$
6f	216-219	66	<u>56.92</u> 57.13	<u>4.35</u> 4.29	S, <u>15.45</u> 16.05	<u>10.68</u> 10.52	$C_{19}H_{17}N_3O_3S_2$
7a	235—23	64	<u>54.89</u> 54.88	<u>3.67</u> 3.74	Cl, <u>21.00</u> 20.25	<u>11.98</u> 12.00	$C_{16}H_{13}Cl_2N_3O_2$
7b	217-219	76	<u>61.33</u> 61.18	$\frac{3.70}{3.67}$	Cl, <u>17.20</u> 17.05	<u>10.26</u> 10.19	$C_{21}H_{15}Cl_2N_3O_2$
7c	243—244	85	<u>51.61</u> 51.35	$\frac{3.01}{2.87}$	Cl+Br, <u>30.69</u> 30.59	<u>8.61</u> 8.56	$C_{21}H_{14}BrCl_2N_3O_2$
7d	237—239	80	<u>55.16</u> 55.16	<u>3.07</u> 3.09	Cl, <u>15.33</u> 15.51	<u>12.24</u> 12.25	$C_{21}H_{14}Cl_2N_4O_4$
7e	199—202	75	<u>53.86</u> 53.82	<u>3.92</u> 3.72	Cl, <u>18.02</u> 18.65	<u>10.83</u> 11.10	$C_{16}H_{15}Cl_2N_3O_3$
7f	120-125	78	<u>54.43</u> 54.55	<u>3.79</u> 3.71	Cl, <u>15.69</u> 15.33	<u>9.40</u> 9.13	$C_{21}H_{17}Cl_2N_3O_3S$
8a	239—241	98	<u>61.64</u> 61.79	<u>6.54</u> 6.48	_	<u>18.21</u> 18.01	$C_{12}H_{15}N_3O_2$
8b	262—264	73	<u>69.01</u> 69.14	<u>6.03</u> 5.80	_	<u>14.16</u> 14.23	$C_{17}H_{17}N_3O_2$
8c	251-254	87	<u>54.62</u> 54.56	<u>4.55</u> 4.31	Br, <u>21.34</u> 21.35	<u>11.44</u> 11.23	C ₁₇ H ₁₇ BrN ₃ O ₂
8d	273—275	93	<u>59.89</u> 60.00	<u>4.89</u> 4.74	_	<u>16.47</u> 16.46	$C_{17}H_{16}N_4O_4$
8e	217-219	90	<u>59.53</u> 59.30	<u>6.44</u> 6.51	_	<u>15.75</u> 15.96	$C_{13}H_{17}N_3O_3$
8f	185—189	79	<u>59.14</u> 59.11	<u>5.63</u> 5.54	S, <u>9.54</u> 9.28	<u>12.19</u> 12.22	$C_{17}H_{19}N_3O_3S$
9a	234—236	85	<u>65.64</u> 65.91	<u>6.94</u> 7.01	_	<u>15.49</u> 15.37	$C_{15}H_{19}N_3O_2$
9b	226-229	60	<u>71.55</u> 71.62	<u>6.34</u> 6.31	—	<u>12.67</u> 12.53	$C_{20}H_{21}N_{3}O_{2}$
9c	216-218	75	<u>58.10</u> 57.98	<u>4.88</u> 4.87	Br, <u>19.13</u> 19.29	<u>10.16</u> 10.16	$C_{20}H_{20}BrN_3O_2$
9d	216-220	71	<u>63.34</u> 63.15	<u>5.41</u> 5.30	_	<u>14.95</u> 14 73	$C_{20}H_{20}N_4O_4$
9e	229-232	61	<u>63.34</u> 63.31	<u>6.97</u> 7 01	_	<u>13.74</u> 13.90	$C_{16}H_{21}N_3O_3$
9f	157—164	82	<u>62.25</u> 62.29	<u>5.95</u> 6.01	S, <u>8.27</u> 8.31	<u>10.81</u> 10.89	$C_{20}H_{23}N_3O_3S$

acter and afford 2-substituted 3-acyl- and 3-tosylamido-1,2-dihydroquinazolin-4(3H)-ones **4**—**9** (Scheme 3). The exception is acetophenone, which was not involved in the reaction under these conditions due, apparently, to steric hindrance and low activity of the carbonyl group of this reagent. To the contrary, the low yields in the reactions of hydrazides 2a-f with formaldehyde are associated with high reactivity of the latter reagent and side processes.

Com-	- δ, <i>J</i> /Hz										
pound	N(1)H	HC(2)	C(5)H	C(7)H	C(6)H	C(8)H	N(9)H	R^2, R^3	R ¹		
4 a	6.90 (s)	4.65 (s)	7.65 (d, $J = 8.9$)	7.30 (m)	6.75	5 (m)	10.20 (s)		Ac: 1.90 (s, 3 H)		
4b	6.85 (s)	4.85 (s)	7.70 (d, $J = 10$)	7.33 (t, $J = 9.5$)	6.78	8 (m)	10.75 (s)		Ph: 7.90 (d, 2 H, $J = 10$); 7.60 (t, 1 H, $J = 9.0$); 7.55 (dd, 2 H, $J = 10$, J = 9.0)		
4c	6.81 (s)	4.82 (s)	7.70 (m)	7.30 (dd, J = 9.7, J = 7.5)	6.75	5 (m)	10.80 (s)		$\begin{array}{l} 4 - \text{BrC}_6\text{H}_4: 7.70 \text{ (m, 2 H)}; \\ 7.85 \text{ (d, 2 H, } J = 10) \end{array}$		
4d	6.95 (s)	4.85 (s)	7.70 (d, J = 7.5)	7.35 (dd, J = 8.5,	6.80	0 (m)	11.10 (br.s)		$4-\text{NO}_2\text{C}_6\text{H}_4$: 8.36, 8.15 (both d, 2 H each, J = 9.5)		
4 e	6.75 (m)	4.70 (s)	7.65 (d, $J = 8.6$)	J = 7.0) 7.30 (dd, J = 8.7, J = 7.4)	6.75	5 (m)	9.40 (s)		$CO_2Et: 1.20 (t, 3 H, J = 5.5); 4.10 (q, 2 H, J = 5.5)$		
4f	6.90 (s)	4.15 (s)	7.50 (d, $J = 8.4$)	7.30 (dd, J = 8.5, J = 7.2)	6.70 (dd, J = 8.4, J = 7.2)	6.75 (d, $J = 8.5$)	10.05 (s)		Ts: 2.35 (s, 3 H); 7.30, 7.75 (both d, 2 H each, <i>J</i> = 8.0)		
5a	5.25 (br.s)	4.65 (br.s)	7.85 (d, $J = 9.4$)	7.30 (m)	6.84 (m)	6.65 (d, $J = 9.2$)	8.80 (s)	Me: 1.45 (d, 3 H, $J = 6.7$)	Ac: 2.10 (s, 3 H)		
5b	6.85 (s)	5.70 (q, $J = 8.0$)	7.68 (d, J = 10)	7.30 (t, J = 9.5)	6.74	4 (m)	10.5 (s)	Me: 1.42 (d, 3 H, J = 8.0)	Ph: 7.92 (d, 2 H, <i>J</i> = 10); 7.59 (t, 1 H, <i>J</i> = 9.5); 7.50 (m, 2 H)		
5c	6.84 (s)	5.20 (q, $J = 7.0$)	7.7 (m)	7.30 (m)	6.83	5 (m)	10.60 (s)	Me: 1.42 (d, 3 H, $J = 7.0$)	4-BrC ₆ H ₄ : 7.70 (m, 2 H); 7.85 (d, 2 H, <i>J</i> = 10)		
5d	6.97 (s)	5.23 (q, $J = 7.0$)	7.70 (d, J = 8.4)	7.33 (dd, J = 8.0, J = 6.4)	6.75	5 (m)	10.90 (s)	Me: 1.45 (d, 3 H, J = 7.0)	$4-NO_2C_6H_4$: 8.35, 8.15 (both d, 2 H each, J = 9.2)		
5e	6.82 (s)	5.00 (br.s)	7.64 (d, $J = 8.5$)	7.30 (dd, J = 8.7, J = 7.3)	6.70	0 (m)	9.25 (s)	Me: 1.35 (br.s, 3 H)	CO ₂ Et: 1.20 (br.s, 3 H); 4.10 (q, 2 H, <i>J</i> = 5.3)		
5f	6.95 (s)	4.90 (br.s)	7.45 (d, J = 8.4)	7.25 (dd, J = 8.6, J = 7.2)	6.70 (dd, J = 8.4, J = 7.2)	6.65 (d, $J = 8.6$)	10.00 (s)	Me: 1.30 (br.s, 3 H)	Ts: 2.35 (s, 3 H); 7.30, 7.70 (both d, 2 H each, <i>J</i> = 8.1)		
6a	7.10 (br.s)	6.22 (s)	7.70 (d, J = 8.1)	7.30 (m)	6.75 (m)	9.90 (s)		3 CH: 6.95 (s, 1 H); 7.45 (m, 2 H)	Ac: 1.80 (s, 3 H)		
6b	7.18 (s)	6.42 (s)	7.72 (m)	7.35 (dd, J = 9.5, J = 8.0)	6.8 (dd, J = 8.8, J = 8.0)	6.85 (d, J = 9.5)	10.45 (s)	3 CH: 6.95 (m, 1 H); 7.45 (m, 1 H); 7.55 (m, 1 H)	Ph: 7.72 (m, 2 H); 7.45 (m, 3 H)		
6c	7.15 (s)	6.40 (s)	7.73 (d, J = 8.7)	7.35 (dd, J = 8.5, J = 7.3)	6.85 (dd, J = 8.7, J = 7.3)	6.80 (d, $J = 8.5$)	10.60 (s)	3 CH: 6.95 (m, 1 H); 7.50 (m, 2 H)	4-BrC ₆ H ₄ : 7.70 (m, 2 H); 7.75 (d, 2 H, <i>J</i> = 9.6)		
6d	7.19 (br.s)	6.45 (s)	7.75 (d, $J = 7.7$)	7.35 (dd, $J = 8.4$	6.63 (dd, $J = 7.7$	6.75 (d, $J = 8.4$)	10.95 (s)	3 CH: 6.95 (m 1 H):	$4-NO_2C_6H_4$: 8.33, 8.0 (both d. 2 H each		
	(01.3)	6.00		J = 6.7)	J = 6.7	у то т)	0.00	7.50 (m, 2 H)	J = 8.4		
6e	7.43 (s)	6.20 (s)	7.68 (d, $J = 8.4$)	7.35 (dd, J = 8.5, J = 7.2)	6.75 (dd, J = 8.4, J = 7.2)	6.85 (d, J = 8.5)	9.30 (br.s)	3 CH: 7.00 (m, 1 H); 7.16 (m, 1 H); 7.52 (d, 1 H, <i>J</i> = 4.8)	$CO_2Et: 1.15 (t, 3 H, J = 5.6); 4.05 (q, 2 H, J = 5.6)$		

Table 2. ¹H NMR spectroscopic data (in DMSO-d₆) for 1,2-dihydroquinazolin-4(3*H*)-one derivatives **4**–9

(to be continued)

Table 2 (continued)	e 2 (continu	ued)	
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Com-	- δ, <i>J</i> /Hz									
pound	N(1)H	HC(2)	C(5)H	C(7)H	C(6)H	C(8)H	N(9)H	R^2, R^3	R ¹	
6f	7.05 (br.s)	6.20 (s)	7.45 (d, $J = 8.4$)	7.30 (dd, J = 8.8, J = 7.0)	6.65 (dd, J = 8.4, J = 7.0)	6.75 (d, J = 8.8)	10.40 (s)	3 CH: 6.95 (m, 1 H); 7.25 (m, 1 H); 7.36 (d, 1 H, <i>I</i> = 5 3)	Ts: 2.35 (s, 3 H); 7.30, 7.75 (both d, 2 H each, <i>J</i> = 8.2)	
7a	7.30 (br.s)	6.40 (s)	7.65 (m)	7.35 (m)	6.75 (m)		9.85 (s)	(d, 1 H, $J = 5.5$) 3 CH: 7.50 (d, 1 H, $J = 9.6$); 7 65 (m 2 H)	Ac: 1.75 (s, 3 H)	
7b	7.25 (s)	6.61 (s)	7.84 (d, J = 9.2)	7.33 (dd, J = 9.1, J = 8.0)	6.78 (m)		10.38 (s)	3 CH; 7.45 (d, 1 H, J = 9.5); 7.50 (s, 1 H); 7.72 (d, 1 H, J = 9.5)	Ph: 7.68 (d, 2 H, <i>J</i> = 9.4); 7.50 (m, 1 H); 7.42 (dd, 2 H, <i>J</i> = 9.4, <i>J</i> = 8.9)	
7c	7.22 (s)	6.60 (s)	7.82 (d, J = 10.1)	7.32 (dd, J = 8.6, J = 7.4)	6.75 (m)		10.45 (s)	3 CH: 7.42 (d, 1 H, <i>J</i> = 9.5); 7.44 (s, 1 H); 7.72 (d, 1 H, <i>J</i> = 9.5)	$4-BrC_6H_4$: 7.60, 7.65 (both d, 2 H each, J = 9.6);	
7d	7.27 (s)	6.65 (s)	7.85 (d, $J = 8.5$)	7.35 (m)	6.80) (m)	10.80 (s)	3 CH: 7.50 (m, 2 H); 7.75 (d, 1 H, J = 9.3)	$4-NO_2C_6H_4$: 8.35, 8.05 (both d, 2 H each, J = 8.5)	
7e	7.20 (s)	6.41 (s)	7.50 (d, $J = 8.4$)	7.30 (dd, J = 8.0, J = 7.2)	6.75 (m)		9.20 (s)	3 CH: 7.68 (s, 1 H); 7.70 (m, 2 H)	$CO_2Et: 1.15 (t, 3 H, J = 5.5); 4.00 (q, 2 H, J = 5.5)$	
7f	7.15 (br.s)	6.35 (s)	7.45 (d, $J = 8.4$)	7.25 (m)	6.70 (m)		10.35 (s)	3 CH: 7.50 (br.s, 2 H); 7.65 (s, 1 H)	Ts: 2.35 (s, 3 H); 7.30, 7.70 (both d, 2 H each, <i>J</i> = 8.1)	
8a	6.95 (s)		7.60 (d, $J = 8.8$)	7.30 (m)	6.70) (m)	9.75 (s)	2 Me: 1.38, 1.42 (both s, 3 H each)	Ac: 1.90 (s, 3 H)	
8b	6.85 (s)		7.64 (d, J = 9.0)	7.28 (t, J = 9.5)	6.72	! (m)	10.20 (s)	2 Me: 1.52 (s, 6 H)	Ph: 7.92 (d, 2 H, <i>J</i> = 7.6); 7.58 (t, 1 H, <i>J</i> = 8.0); 7.50 (dd, 2 H, <i>J</i> = 8.0, <i>J</i> = 7.6)	
8c	6.90 (s)		7.65 (d, J = 9.2)	7.28 (dd, J = 9.0, J = 7.2)	6.70) (m)	10.20 (s)	2 Me: 1.50 (s, 6 H)	4-BrC ₆ H ₄ : 7.70, 7.85 (both d, 2 H each, J = 9.8)	
8d	6.90 (s)		7.65 (d, $J = 8.5$)	7.30 (dd, J = 8.8, J = 7.0)	6.72	2 (m)	10.55 (s)	2 Me: 1.52 (s, 6 H)	$4-NO_2C_6H_4$: 8.35, 8.15 (both d, 2 H each, J = 9.1)	
8e	6.95 (s)		7.65 (d, J = 8.5)	7.30 (dd, J = 8.6, J = 7.2)	6.70 (m)		9.20 (s)	2 Me: 1.35, 1.45 (both s, 3 H each)	CO ₂ Et: 1.10 (br.s, 3 H); 4.20 (m, 2 H)	
8f	6.95 (s)		7.45 (d, J = 8.8)	7.25 (dd, J = 9.2, J = 7.0)	6.70 (dd, J = 8.8, J = 7.0)	6.60 (d, J = 9.2)	9.60 (s)	2 Me: 1.25, 1.50 (both s, 3 H each)	Ts: 2.35 (s, 3 H); 7.30, 7.65 (both d, 2 H each, <i>J</i> = 8.0)	
9a	6.65 (s)		7.62 (d, $J = 8.4$)	7.25 (m)	6.70 (m)	6.95 (d, $J = 9.4$)	9.55 (s)	(CH ₂) ₅ : 1.65 (m, 10 H)	Ac: 1.95 (s, 3 H)	
9b	7.05 (s)		7.65 (d, $J = 8.25$)	7.35 (m)	6.75	5 (m)	10.25 (s)	(CH ₂) ₅ : 1.65 (m, 10 H)	Ph: 7.95 (d, 2 H, <i>J</i> = 7.5); 7.60 (t, 1 H, <i>J</i> = 8.0); 7.50 (dd, 2 H, <i>J</i> = 8.0, <i>J</i> = 7.5)	

(to be continued)

Com-	δ, <i>J</i> /Hz												
pound	N(1)H HC(2)	C(5)H	C(7)H	C(6)H	C(8)H	N(9)H	R^2, R^3	\mathbf{R}^1					
9c	6.70 (s)	7.65 (d, $J = 8.5$)	7.28 (dd, J = 8.8, J = 7.0)	6.68 (dd, J = 8.5, J = 7.0)	7.00 (d, $J = 8.8$)	10.25 (s)	(CH ₂) ₅ : 1.75 (m, 10 H)	4-BrC ₆ H ₄ : 7.68, 7.88 (both d, 2 H each, J = 9.9)					
9d	6.85 (m)	7.68 (d, $J = 8.3$)	7.35 (m)	6.85 (m)	7.05 (d, $J = 8.7$)	10.55 (s)	(CH ₂) ₅ : 1.75 (m, 10 H)	$4-NO_2C_6H_4$: 8.4, 8.15 (both d, 2 H each, J = 9.1)					
9e	6.70 (m)	7.60 (d, $J = 8.0$)	7.30 (dd, J = 8.0, J = 7.6)	6.70 (m)	6.95 (d, $J = 8.0$)	9.05 (s)	(CH ₂) ₅ : 1.75 (m, 10 H)	CO ₂ Et: 1.20 (br.s, 3 H); 4.05 (m, 2 H)					
9f	6.55 (m)	7.42 (d, $J = 8.4$)	7.25 (m)	6.55 (m)	6.85 (d, $J = 8.6$)	9.10 (s)	(CH ₂) ₅ : 1.75 (m, 10 H)	Ts: 2.40 (s, 3 H); 7.25 (m, 2 H); 7.65 (d, 2 H, J = 8.0)					

Table 2 (continued)

The structures of compounds 4-9 were established by the comprehensive examination of the spectroscopic data and the results of elemental analysis.

Analysis of the results of our study indicates that these compounds have structures of the same type. In particular, to establish whether these compounds have structures **A** or **B**, we carried out nuclear Overhauser effect (NOE) measurements and



 $R^3 = H (4-7), Me (8), R^2-R^3 = (CH_2)_5$

experiments on selective proton magnetization transfer (SPT) from the methyl group $C(12)H_3$ to ¹³C nuclei and from the proton of the N(10)H group to the carbonyl C(11) atom (Scheme 4) for compound **8a**.

Scheme 4



The results of these studies provide evidence that the atoms of the following groups are closely spaced: N(1)H and H(8) (*a*), N(1)H and C(2)<u>C</u>H₃ (*b*), C(2)<u>C</u>H₃ and N(9)H (*c*), N(9)H and COC(11)H₃ (*d*), COC(11)H₃ and C(10)O (*e*), and N(9)H and C(10)O (*f*). The observed

NOEs can belong only to a compound with structure **A**, but not to a compound with structure **B**.

For compounds with structure **B**, NOEs c, d, and f should not be observed, but the interaction between the carbonyl group of the fragment of the aminobenzoic acid and the NH group of the hydrazide fragment could be seen.

The choice between the structures of DHQ and isomeric Schiff's bases can reliably be made using the ¹H and ¹³C NMR spectroscopic data for these compounds. The most general and pronounced feature of these spectra is the presence of signals of the C(2)H-group protons of DHQ at $\delta 4.82 - 5.23$ and $\delta 6.40 - 6.65$ for adducts derived from aliphatic aldehydes and products derived from aromatic aldehydes, respectively (see Table 2), which is characteristic of the corresponding protons of 1,2-dihydroquinazolin-4(3H)-ones.^{13,14} On the contrary, if adducts derived from aromatic aldehydes had structures of Schiff's bases, signals of the CH=N-group protons should be observed at $\delta 8.2 - 8.5$.¹⁵ However, no signals are present in this area of the spectra of compounds 4-9 (except for compounds 4d-9d, whose spectra have signals of the aromatic ring containing the nitro group).

To establish the structures of the products of the reactions with ketones **8** and **9**, it was necessary to measure ${}^{13}C$ NMR spectra because these compounds are devoid of protons at the C(2) atoms, and, hence, their structures cannot be determined only by ¹H NMR spectroscopy. For Schiff's bases, the signals of the <u>CH=N-group</u> carbon atom are generally observed at δ 157–164, ¹⁶ whereas the signals of the C(2) atom in compounds **8** and **9** are present at δ 67–76 (see Table 3), which agrees with the DHQ structure (δ (C(2)) 68.7)¹³.

Other spectroscopic characteristics of the compounds under study are also in agreement with the DHQ structure. The ¹H NMR spectra have signals for the protons of the N(1)H and N(9)H groups at δ 6.7–7.25 and

Com-							δ, <i>J</i> /Ι	Ηz		
pound	C(2)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)	R^2, R^3	R ¹
5a	67.8	168.9	114.1	134.0	114.8	128.2	117.7	148.0	1 Me: 19.5	COMe: 20.3 (Me), 162.8 (CO)
5c	67.8	165.0	114.0	133.9	114.7	128.1	117.7	148.0	1 Me: 19.4	4-BrC ₆ H ₄ : 162.9, 131.4, 129.7, 126.0, 131.7
8a	74.3	169.5	113.3	133.9	114.6	127.8	117.2	146.3	2 Me: 25.7, 26.3	COMe: 20.6 (Me), 161.4 (CO)
8b	74.5	166.4	113.5	133.6	114.5	127.6	116.9	146.3	2 Me: 26.0, 26.4	Ph: 161.1, 132.6, 128.3, 131.7, 127.5
8c	74.7	165.8	113.5	134.0	114.7	127.9	117.2	146.5	2 Me: 26.1, 26.5	4-BrC ₆ H ₄ : 161.3, 131.7, 129.9, 125.8, 131.6
8d	74.9	165.4	113.4	134.1	114.8	128.0	117.3	146.6	2 Me: 26.1, 26.6	4-NO ₂ C ₆ H ₄ : 161.4, 138.4, 129.4, 149.6, 123.9
8e	74.7	162.1	113.5	134.2	114.9	128.1	117.4	146.7	2 Me: 26.1, 26.8	CO ₂ Et: 156.9 (CO), 61.1 (CH ₂), 14.8 (Me)
8f	75.3	164.4	112.4	134.2	114.6	127.8	116.9	146.4	2 Me: 27.8, 23.4	Ts: 21.1, 129.0, 127.6, 142.8, 137.1
9a	75.4	169.3	114.2	133.6	115.2	127.6	117.2	145.6	(CH ₂) ₅ : 20.9, 21.3, 24.4, 32.5, 33.3	COMe: 161.6 (CO), 20.7 (Me)
9b	76.0	166.8	114.6	133.8	115.5	127.8	117.5	145.9	(CH ₂) ₅ : 21.5, 21.4, 24.6, 33.0, 33.6	Ph: 161.7, 132.8, 128.6, 132.1, 127.9
9c	75.9	165.9	114.4	133.8	115.0	127.7	117.4	148.8	(CH ₂) ₅ : 21.0, 21.3, 24.4, 32.9, 33.5	4-BrC ₆ H ₄ : 161.6, 131.6, 129.9, 125.8, 131.6
9d	75.7	165.1	114.8	133.5	115.3	127.4	117.2	145.5	(CH ₂) ₅ : 20.9, 21.1, 24.2, 32.7, 33.3	4-NO ₂ C ₆ H ₄ : 161.2, 138.2, 129.0, 149.3, 123.4
9e	75.9	162.5	114.3	134.1	115.6	127.9	117.6	146.0	(CH ₂) ₅ : 21.2, 21.6, 24.8, 32.8, 33.7	CO ₂ Et: 157.0 (CO), 61.1 (CH ₂), 14.9 (Me)
9f	76.2	164.2	113.2	133.7	115.1	127.3	116.9	142.6	(CH ₂) ₅ : 20.8, 21.4, 24.1, 30.0, 34.4	Ts: 20.7, 127.5, 128.4, 145.3, 136.9

Table 3. ¹³C NMR spectroscopic data for 1,2-dihydroquinazolin-4(3H)-one derivatives 5–9 (in DMSO-d₆)

 δ 10.1–10.78, respectively. Since, all signals of the NH group of the seven-membered triazepine isomer should be observed at δ 6.7–9.0,⁵ its formation can be excluded as well.

3-Acyl- and 3-tosylamido-2-R-1,2-dihydroquinazolin-4(3*H*)-ones were synthesized as crystalline compounds (from colorless to bright-yellow in color) with the melting points varying from 160 to 275 °C depending on the nature of substituents at positions 2 and 3.

When investigating¹⁷ the reactions of quinazolinone derivatives with BuLi, the researchers of the cited study prepared a compound to which structure **5a** was assigned. However, the latter compound differs from quinazolinone **5a** prepared in the present study both in the spectroscopic characteristics and melting point (the difference is larger than 80 °C). Hence, we studied compound **5a** (its crystals were grown from an aqueous solution) by X-ray diffraction analysis, which confirmed the structure of this compound.

X-ray diffraction study demonstrated that quinazolinone **5a** crystallizes with one water molecule of solvation as a racemate (space group $P2_1/c$). The selected bond lengths and bond angles in compound **5a** are close to the expected values (Fig. 1, Table 4). The nitrogen-contain-



Fig. 1. Overall view of molecule 5a.

ing ring adopts a slightly distorted envelope conformation with the C(8) atom deviating from the plane through the remaining atoms of the ring by 0.6 Å. The N(1) atom has a pyramidal configuration (the sum of the bond angles is 350.3°). A shortening of the N(1)—C(7) bond to 1.381 Å is, apparently, caused by conjugation between the lone electron pair of the N(7) atom and the aromatic system of the benzene ring. The same situation has been observed earlier in an analog of **5a**, *viz.*, 2,2-dimethyl-3-(1-methylethylidene)amino-4-oxo-1,2,3,4-tetrahydro-

Bond	$d/\text{\AA}$	Angle	ω/deg
O(1)-C(1)	1.230(1)	C(7)-N(1)-C(8)	116.9(1)
O(2)-C(10)	1.224(1)	C(1) - N(2) - N(3)	115.89(9)
N(1) - C(7)	1.380(1)	C(1) - N(2) - C(8)	120.83(9)
N(1) - C(8)	1.445(2)	N(3) - N(2) - C(8)	115.38(9)
N(2) - C(1)	1.378(1)	C(10) - N(3) - N(2)	118.8(1)
N(2) - N(3)	1.390(1)		
N(2) - C(8)	1.487(1)		
N(3)-C(10)	1.358(2)		

Table 4. Principal bond lengths (*d*) and bond angles (ω) in the structure of **5a**

quinazoline.¹⁸ The dihedral angle between the amide fragment and the base of the envelope is 65.1°.

Analysis of the crystal packing demonstrates that molecules **5a** do not form intermolecular hydrogen bonds with each other but are linked in a three-dimensional H-bound framework through the weak N-H...O(1w) and O(1w)-H(1w)...O bonds with the water molecules (N...O, 2.902(2)-3.042(2) Å; O...O, 2.719(2)...2.822(2) Å) (Fig. 2). Taking into account these hydrogen bonds, the coordination environment of the O(1w) atom can be described as a slightly distorted tetrahedron.

Experimental

The IR spectra were recorded on an M80 spectrometer in KBr pellets. The ¹H NMR spectra were measured on Bruker

DRX 500 (500 MHz) and Bruker AM-300 (300 MHz) spectrometers. The ¹³C NMR spectra were recorded on a Bruker WM-250 spectrometer (62.9 MHz for ¹³C). The melting points were measured on a Boetius hot-stage apparatus and were uncorrected. The yields and physicochemical data for products 2a-f are given in Table 5. The corresponding characteristics of compounds 4-9 are listed in Tables 1–3. Compounds 1a-fwere prepared according to known procedures.¹⁰

Single-crystal X-ray diffraction study of compound 5a was carried out on an automated Siemens P3/PC diffractometer (graphite monochromator, λ (MoK α) = 0.71073 Å, $\theta/2\theta$ scanning technique, $\theta_{\text{max}} = 26^{\circ}$). Crystals of **5a** (C₁₁H₁₃N₃O₂ · H₂O, M = 237.26) are monoclinic, space group $P2_1/c$, at T = 293 K a = 8.178(4), b = 9.746(9), c = 15.013(3) Å, $\beta = 93.96(3)^{\circ}$, V = 1193.9(4) Å³, Z = 4, $d_{calc} = 1.320$ g cm⁻³. The structure of 5a was solved by direct methods and refined by the full-matrix least-squares method based on F_{hkl}^2 with anisotropic thermal parameters for all nonhydrogen atoms. The hydrogen atoms were revealed from a difference electron density synthesis and refined isotropically. The final reliability factors were as follows: $R_1 = 0.0387$ (based on F^2 for 2332 observed reflections with $I > 2\sigma(I)$, $wR_2 = 1049$, GOOF = 0.905, 214 parameters were refined. The calculations were carried out on a personal computer using the SHELXTL PLUS program package.²¹

Synthesis of N'-acetyl- (2a), N'-benzoyl- (2b), N'-(4-bromobenzoyl)- (2c), N'-(4-nitrobenzoyl)- (2d), and N'-ethoxycarbonylhydrazides (2e) of 2-aminobenzoic acid (general procedure). A mixture of isatoic anhydride (0.04 mol) and the corresponding hydrazide 1a-d (0.04 mol) in acetic acid (30 mL) (the reaction with 1e was carried out in anhydrous EtOH (30 mL)) was stirred with refluxing for 1 h and then cooled to ~20 °C for 2 h. The precipitate that formed was filtered off, washed with Et₂O, and dried at 40 °C.



Fig. 2. Intermolecular hydrogen bonds in the crystal structure of 5a.

Com-	m.p./°C	Yield				â	δ, <i>J</i> /Hz		
pound	(m.p.*/°C)	(%)	C(5) <u>H</u>	C(6) <u>H</u>	C(7) <u>H</u>	C(8) <u>H</u>	NH ₂	NHNH	R
2a	181 (181) ¹⁹	57	7.50 (d, $J = 8.8$)	6.50 (m)	7.20 (m)	6.75 (d, $J = 9.5$)	6.40 (br.s)	9.85 (br.s); 9.95 (br.s)	COMe: 1.90 (s, 3 H)
2b	177—179 (179) ⁵	59	7.55 (m)	6.55 (m)	7.20 (m)	6.75 (d, $J = 9.2$)	6.45 (br.s)	10.1 (br.s); 10.32 (s)	COPh: 7.55 (m, 3 H); 7.95 (d, 2 H, <i>J</i> = 9.8)
2c**	216-218	70	7.60 (d, $J = 8.0$)	6.60 (m)	7.20 (m)	6.75 (d, J = 9.3)	6.35 (br.s)	10.20 (br.s); 10.40 (br.s)	4-BrCOC ₆ H ₄ : 7.75, 7.90 (both d, 2 H each, <i>J</i> = 9.5)
2d	238—240 (238) ⁵	81	7.60 (d, J = 8.4)	6.55 (dd, J = 8.4, J = 6.4)	7.20 (dd, J = 8.6, J = 6.4)	6.75 (d, $J = 8.6$)	6.42 (s)	10.25 (br.s); 10.70 (s)	4-NO ₂ COC ₆ H ₄ : 8.15, 8.35 (both d, 2 H each, <i>J</i> = 9.1)
2e	117 (117) ²⁰	70	7.50 (d, J = 8.6)	6.50 (dd, J = 8.6, J = 6.8)	7.20 (dd, J = 8.8, J = 6.8)	6.75 (d, $J = 8.8$)	6.40 (br.s)	9.00 (br.s); 9.85 (s)	EtCO ₂ : 1.10 (t, 3 H, J = 5.6); 4.00 (q, 2 H, J = 5.6)
2f	196—198 (198) ¹¹	75	7.45 (d, J = 8.5)	6.50 (dd, J = 8.5, J = 7.0)	6.70 (dd, J = 9.3, J = 7.0)	7.15 (d, J = 9.3)	6.10 (br.s)	9.65 (s); 10.30 (br.s)	Ts: 2.40 (s, 3 H); 7.40, 7.75 (both d, 2 H each, <i>J</i> = 8.2)

Table 5. Yields, physicochemical properties, and ¹H NMR spectroscopic data (in DMSO-d₆) for 2-aminobenzoic acid N'-acyl- and N'-tosylhydrazides **2a**-f

* Lit. data.

** Found/calculated: C, 50.32/50.63; H, 3.62/3.78; Br, 23.91/23.9; N, 12.58/12.31. C₁₄H₁₂BrN₃O₂.

Upon more prolonged storage of a solution of **2c** in AcOH, a precipitate formed. This precipitate was filtered off, recrystallized from 95% EtOH, and dried. **2-(4-Bromophenyl)-3,4-dihydro-1,3,4-benzotriazepin-5-one** (**3**) was prepared in 6.2% yield. M.p. 195–196 °C. Found (%): C, 53.39; H, 3.29; Br, 25.57; N, 13.48. Calculated (%): C, 53.19; H, 3.19; Br, 25.27; N, 13.29. ¹H NMR (DMSO-d₆), & 5.63 (s, 2 H, 2 NH); 7.55 (m, 1 H, CH(6)); 7.35 (m, 1 H, CH(7)); 7.75 (m, 1 H, CH(5)); 7.65 (d, 2 H, 4-BrC₆H₄, J = 7.9 Hz); 7.80 (d, 2 H, 4-BrC₆H₄, J = 7.9 Hz).

Synthesis of 3-acyl- and 3-tosylamido-1,2-dihydroquinazolin-4(3*H*)-ones (4a–f) (general procedure). A mixture of the corresponding hydrazide 2a-f (2 mmol), CH₂O as paraformaldehyde (3 mmol, 1.5-fold excess), and K₂CO₃ (10 mg) was refluxed in 95% EtOH for 2 h. The reaction solution was concentrated and the residue was recrystallized from a hexane—benzene (1 : 1) (4a), 95% EtOH—hexane (1 : 1) (4b), or 95% EtOH—benzene (1 : 3) (4c–f) mixture.

Synthesis of tosylhydrazide (2f). Compound 2f was synthesized according to a procedure described earlier.¹¹ The physicochemical characteristics and NMR spectra are identical with the data published in the literature.¹¹ M.p. 196–198 °C (*cf.* lit. data¹¹: 198 °C). Found (%): C, 55.01; H, 4.95; N, 13.80; S, 10.24. $C_{14}H_{15}N_{3}O_{3}S$. Calculated (%): C, 55.07; H, 4.95; N, 13.76; S, 10.50.

Synthesis of 3-acyl- and 3-tosylamido-2-methyl-1,2dihydroquinazolin-4(3H)-ones (5a-f) (general procedure). Acetaldehyde (20 mmol, 10-fold excess) was added to a solution of the corresponding hydrazide 2a-f (2 mmol) in 95% EtOH (20 mL). The reaction mixture was stirred in a closed flask at ~20 °C for 4 h and then concentrated. The oily residue was recrystallized from a benzene—hexane mixture. Synthesis of 3-acyl- and 3-tosylamido-2-R-1,2-dihydroquinazolin-4(3H)-ones (6a-f, 7a-f, 9a-f) (general procedure). A mixture of the corresponding hydrazide 2a-f (1.7 mmol) and a carbonyl compound (2 mmol, a 1.2-fold excess) in 95% EtOH (15 mL) was refluxed for 3-6 h. Then the reaction mixture was cooled and the precipitate that formed was recrystallized from a 95% EtOH—benzene mixture.

Synthesis of 3-acyl- and 3-tosylamido-2,2-dimethyl-1,2dihydroquinazolin-4(3H)-ones (8a–f). A solution of the corresponding hydrazide 2a-f(1.7 mmol) in acetone (20 mL), which was distilled over KMnO₄, was refluxed for 5 h. Then the reaction solution was concentrated and the residue was recrystallized from a 1 : 1 benzene—hexane mixture.

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