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REACTION OF BARBITURIC, 2-THIOBARBITURIC ACIDS AND THEIR DERIVATIVES WITH 2-CARBOXYBENZALDEHYDE AND OPIANIC ACID: SYNTHESIS AND TAUTOMERISM OF 5-(3'-OXO-1',3'-DIHYDRO-ISOBENZOFURAN-1'-YL)BARBITURIC ACIDS AND THEIR 2-THIO ANALOGS

K. A. Krasnov[1], V. G. Kartsev[2], and E. E. Santarovich[1]

The reaction of barbituric, N-alkylbarbituric acids, and their 2-thio analogs with carboxybenzaldehyde and 2-carboxy-3,4-dimethoxybenzaldehyde leads to the formation of the corresponding 5-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)barbituric and 2-thiobarbituric acids, the structures of which were studied by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. In DMSO the derivatives of barbituric acid exist in the form of mixtures of the ketone and enol tautomers, while their 2-thio analogs exist in the enol form. In chloroform the tautomeric equilibrium is displaced fully toward the ketone form.

Keywords: barbituric acids, 2-carboxybenzaldehydes, 5-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)-barbituric acids, 2-thio analogs.

It is well known that aromatic and heteroaromatic aldehydes react with barbituric acids having an unsubstituted methylene group with the formation of 5-arylidenebarbituric acids [1], and in the case of 2-thiobarbituric acids the formation of the corresponding bispyrimidinylmethanes is also possible [2]. The only exception is the reaction of barbituric acids with salicylaldehyde and its analogs, leading to the production of tricyclic benzopyranopyrimidine systems [3]. The reaction of barbituric acid and its derivatives with 2-carboxybenzaldehyde and 2-carboxy-3,4-dimethoxybenzaldehyde, known as opianic acid, has not been described in the literature.

We established that instead of the expected 5-benzylidenebarbituric acids **3** the reactions of barbituric (**1a**) and 1,3-dimethylbarbituric (**1b**) acids with 2-carboxybenzaldehyde (**2a**) give 5-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)barbituric acid (**4a**) and its 1,3-dimethyl derivative **4b** respectively. Similarly, in the reaction of opianic acid (**2b**) with the acids **1a**,**b** we obtained 5-(4',5'-dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)barbituric acids (**4c**,**d**). The structure of these products was proved on the basis of the mass spectra and ^{1}H and ^{13}C NMR spectra. The molecular masses, determined for the compounds **4a-d**, rule out

[1] I. I. Mechnikov St. Petersburg State Medical Academy, St. Petersburg, Russia; e-mail: viselkoff@mail.ru. [2] OOO InterBioSkrin, Moscow, Russia; e-mail: screen@nsp.chg.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 798-806, June, 2002. Original article submitted June 9, 2000. Revision submitted March 5, 2001.

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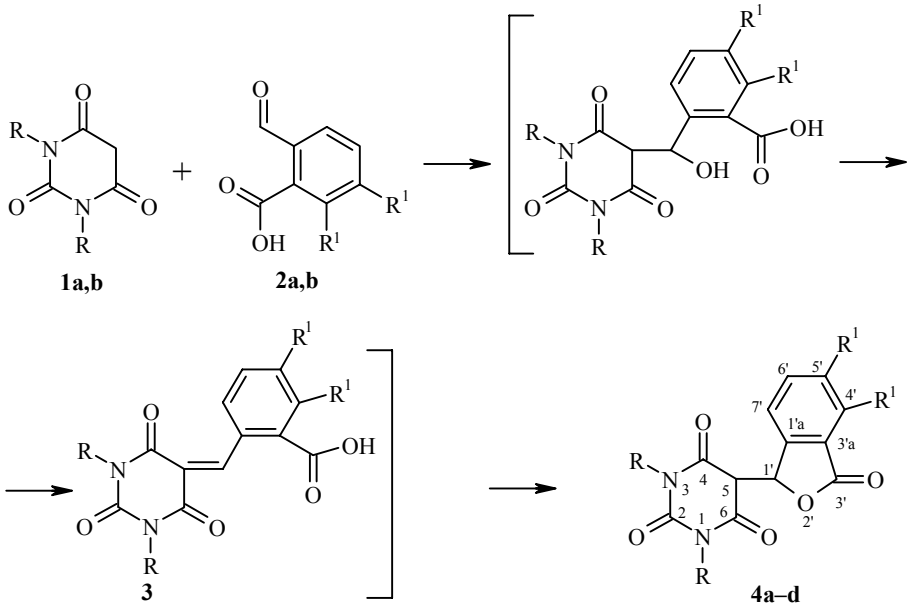


1a,b **2a,b** **3** **4a–d**

1 a R = H, **b** R = Me; **2 a** R^1 = H, **b** R^1 = OMe; **4 a**, **c** R = H; **b**, **d** R = Me; **a**, **b** R^1 = H; **c**, **d** R^1 = OMe

the possibility of the existence of the bispyrimidinylmethane structure and indicate that their formation is accompanied by the elimination of one water molecule. In the ^{1}H NMR spectrum of compound **4b**, recorded in deuterochloroform solution, there are no signals in the region of 8.0-8.5 ppm characteristic of the vinyl protons of 5-benzylidene derivatives **3** [4]. At the same time there are signals for the H-5 protons of the pyrimidine fragment at 4.12 ppm and H-1 of the lactone fragment at 6.24 in the form of doublets with J = 2.2 Hz (Table 1). Singlets at 3.14 and 3.30 ppm correspond to the protons of the NCH_3 groups, the nonequivalence of which is due to interaction between the pyrimidine ring and the asymmetric benzofuran fragment of the molecule. In the ^{13}C NMR spectrum of compound **4b** (Table 2) there are a signal at 51.51 ppm, typical for the sp^3-hybridized C-5 atom of barbituric acids [5], and signals for the C-1' (79.05 ppm) and C-3' (169.10 ppm) atoms, indicating lactonization of the carboxybenzaldehyde fragment. Similarly, the spectral data for compound **4d** confirm its structure unambiguously.

The mechanism of the reactions of barbituric acids with 2-carboxybenzaldehydes probably includes several stages, at one of which the 5-*o*-carboxybenzylidene derivative **3** is formed. This undergoes intramolecular addition of a carboxy group to the activated double bond with the formation of the final products **4**. It was not possible to isolate the intermediate products **3**, but the proposed mechanism is favored by the fact that when solutions of the barbituric acids and the benzaldehyde **2b** are mixed there appears a yellow color (λ_{max} ~405 nm), characteristic of 5-alkoxybenzylidenebarbituric acids, which have strong absorption bands in the region of 390-420 nm [6]. As the reaction proceeds, the intensity of the color at first increases and then decreases, since the final products do not absorb in the visible region of the spectrum.

From the N-alkyl- and N-arylbarbituric acids **5a-h** in reaction with benzaldehyde **2b** we obtained the corresponding N-substituted 5-(4',5'-dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)barbituric acids **6a-h**.

Similarly, from 2-thiobarbituric acid (**7a**) and its N-alkyl derivatives **7b**,**c** we synthesized the 2-thio analogs of this series **8a-e**.

TABLE 1. The ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Solvent	Tautomeric form, %	Chemical shift, δ, ppm, and SSCC, *J*, Hz				
			O(4')Me, O(5')Me	H-5	H-1'	H_{Ar}	NH (NCH–)
1	2	3	4	5	6	7	8
4a	DMSO-d_6	Ketone, 60	—	4.54, s (br.)	6.12, s (br.)	6.65-8.10 m	11.45, s; 11.60, s
		Enol, 40	—	—	6.35-6.80	6.65-8.10 m	10.85, s
4b	DMSO-d_6	Ketone, 62	—	4.88, s (br.)	6.36, s (br.)	7.35-8.15 m	(3.08, s; 3.21, s)
		Enol, 38	—	—	6.40-7.10	7.35-8.15 m	(3.20, s)
	$CDCl_3$	Ketone, 100	—	4.12, d, *J* = 2.2	6.24, d, *J* = 2.2*	7.51, d, *J* = 7.7; 7.56, dd, *J* = 7.7 + 6.7; 7.72, dd, *J* = 7.7 + 6.7; 7.87, d, *J* = 7.7	(3.14, s; 3.30, s)
4c	DMSO-d_6	Ketone, 67	3.88; 3.97	4.50, s (br.)	6.02, s (br.)	7.20-7.40 m	11.40, s; 11.55, s
		Enol, 33	3.99	—	6.30-6.70	7.20-7.40 m	10.90, s
4d	DMSO-d_6	Ketone, 75	3.89; 3.93	4.70, s (br.)	6.07, s (br.)	7.33 m	(3.11, s; 3.22, s)
		Enol, 25	3.96	—	6.45-6.90	7.20 m	(3.23, s)
	$CDCl_3$	Ketone, 100	3.90; 4.07	4.12, d, *J* = 2.3	6.09, d, *J* = 2.3	7.11, d, *J* = 8.1; 7.25, d, *J* = 8.1	(3.17, s; 3.31, s)
6a	DMSO-d_6	Ketone, 55	3.89; 3.94	4.60 + 4.63, s + s	6.08, s (br.)	7.17-7.35 m	(3.06, s); 11.40-11.80, s
		Enol, 45	3.95	—	6.40-6.75	7.17-7.35 m	(3.06, s); 11.15, s
6b	DMSO-d_6	Ketone, 72	3.88; 3.93	4.55, s (br.)	5.99, s (br.)	7.20-7.45 m	(4.20-4.60, m); 11.30-11.70
		Enol, 28	3.93	—	6.25-6.70	7.20-7.45 m	(4.20-4.60, m); 10.96, s
6c	DMSO-d_6	Ketone, 21	3.88; 3.91	4.67 + 4.69, s + s	6.14, s (br.)	7.20-7.30 m	(4.87, s); 11.45, s
		Enol, 79	3.92	—	6.35-6.80	7.20-7.30 m	(4.83, s); 11.05-12.00
6d	DMSO-d_6	Ketone, 33	3.88; 3.92	4.67 + 4.72, s + s	6.08, s (br.)	7.05-7.55 m	11.71, s; 11.85, s
		Enol, 67	3.89-3.95	—	6.40-6.80	7.05-7.55 m	11.27, s

TABLE 1 (continued)

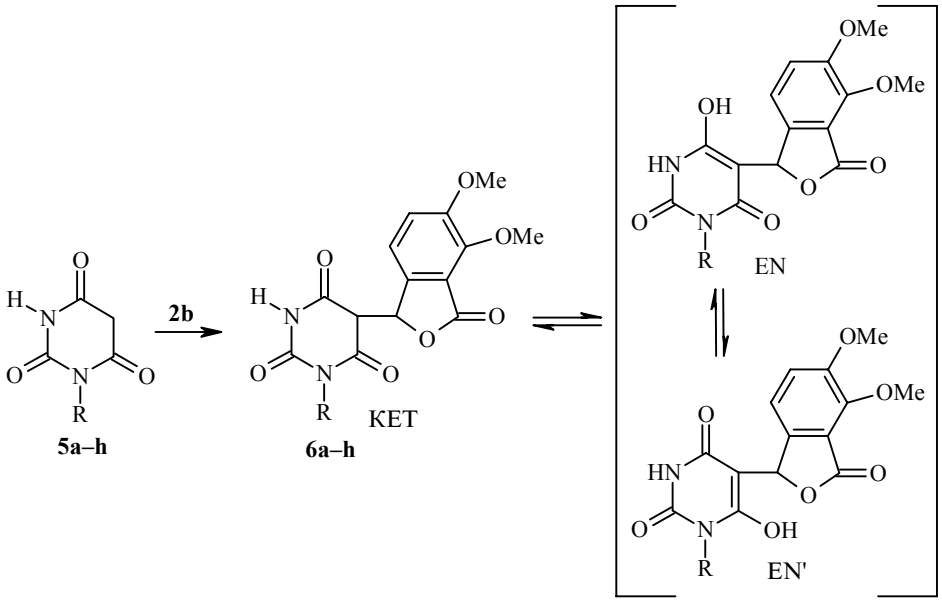
1	2	3	4	5	6	7	8
6e	DMSO-d_6	Ketone, 34 Enol, 66	3.88; 3.91 3.91	4.65 + 4.67, s + s —	6.14, s (br.) 6.45-6.75	7.00-7.35 m 7.00-7.35 m	11.74, s; 11.86, s 11.10-11.95
6f	DMSO-d_6	Ketone, 36 Enol, 64	3.88; 3.93 3.93	4.64 + 4.66, s + s —	6.17, s (br.) 6.55-6.95	6.90-7.35 m 6.90-7.35 m	11.74, s; 11.86, s 11.10-11.95
6g	DMSO-d_6	Ketone, 27 Enol, 73	3.91-3.97 br. 3.94	4.76, s (br.) —	6.05, s (br.) 6.40-6.90	7.18-7.46 m 7.18-7.46 m	11.56, s; 11.80, s 11.50-12.00
6h	DMSO-d_6	Ketone, 25 Enol, 75	3.88; 3.91 3.91	4.70, s (br.) —	6.17, s (br.) 6.40-6.90	7.12-7.60 m 7.12-7.60 m	11.55, s; 11.75, s 11.30-11.90
8a	DMSO-d_6	Enol, 100	—	—	6.76, s	7.30-7.80 m	11.59, s
8b	DMSO-d_6	Enol, 100	3.86; 3.94	—	6.59, s	7.03, d, J = 8.0; 7.22, s (br.)	11.81, s
8c	$CDCl_3$	Ketone, 100	—	4.24, d, J = 2.2	6.27, d, J = 2.2*	7.51, d, J = 6.7; 7.57, dd, J = 7.9 + 6.7; 7.72, dd, J = 7.9 + 6.7; 7.89, d, J = 6.7	(3.52, s; 3.64, s)
	DMSO-d_6	Enol, 100	—	—	6.83, c	7.34, d, J = 8.2; 7.45, dd, J = 8.2 + 7.0; 7.59, dd, J = 8.2 + 7.0; 7.75, d, J = 8.2	(3.49, s)
8d	$CDCl_3$	Ketone, 100	3.90; 4.07	4.09, d, J = 2.1	6.09, d, J = 2.1*	7.11, d, J = 8.1; 7.25, d, J = 8.1	(3.17, s; 3.31, s)
	DMSO-d_6	Enol, 100	3.88; 3.95	—	6.59, s	7.02, d, J = 8.2; 7.21, d, J = 8.2	(3.55, s)
8e	$CDCl_3$	Ketone, 100	3.89, s; 4.05, s	— (under OCH_3)	6.04, d, J = 2.3*	7.10, d, J = 8.2; 7.25, d, J = 8.2	(1.11, t, J = 7.2; 1.17, t, J = 7.2; 4.30, q, J = 7.2; 4.40, q, J = 7.2)
	DMSO-d_6	Enol, 100	3.88, s; 3.95, s	—	6.60, s	7.15, s (br.); 7.15, d, J = 8.1	(1.21, t, J = 6.4; 4.39, q, J = 6.4)

*The signal represents a doublet of doublets with large J = 2.1-2.3 Hz and small J = ~1 Hz.

TABLE 2. The ^{13}C NMR Spectra of Compounds **4b**,**d** and **8c**,**d**

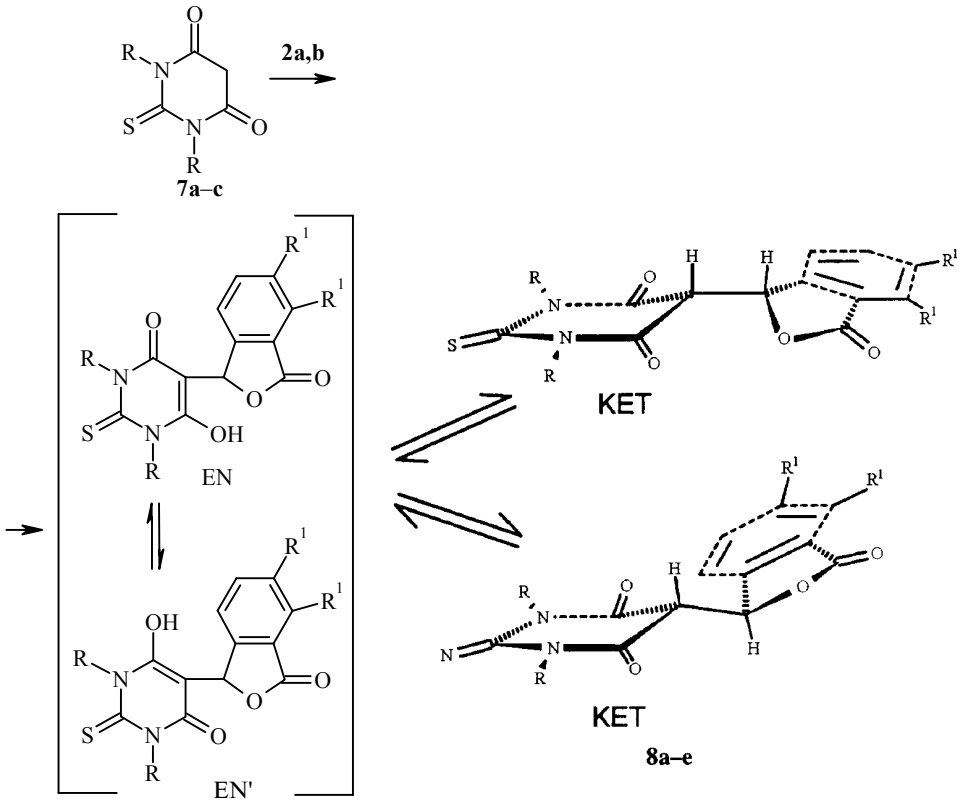
Compound	Solvent	Tautomeric form	Chemical shifts, δ, ppm					
			C-2	C-5	C-4 + C-6	C-1'	C-1'a	C-3'
4b	$CDCl_3$	Ketone	150.84	51.51	163.49+165.65	79.05	146.77	169.10
4d	DMSO-d_6	Ketone	151.72	51.88	161.84+167.40	77.90	140.77	164.80
	$CDCl_3$	Ketone	150.91	52.12	165.79+166.51	78.34	139.21	163.58
8c	DMSO-d_6	Enol	177.88	88.52	161.08	84.64	151.07	171.26
	$CDCl_3$	Ketone	180.19	52.21	162.28+164.14	78.87	146.53	169.12
8d	DMSO-d_6	Enol	177.63	87.90	168.77	80.31	144.38	160.90

Compound	Solvent	Tautomeric form	Chemical shifts, δ, ppm				
			C-3'a	C-4'	C-5'	C-6'	C-7'
4b	$CDCl_3$	Ketone	125.92	129.81	134.50	121.71	125.94
4d	DMSO-d_6	Ketone	119.22	145.03	153.05	120.34	117.98
	$CDCl_3$	Ketone	119.98	148.66	153.13	118.59	116.15
8c	DMSO-d_6	Enol	127.86	128.48	133.91	124.98	122.25
	$CDCl_3$	Ketone	126.01	129.88	134.53	125.97	121.70
8d	DMSO-d_6	Enol	120.46	147.02	151.88	119.73	117.30



a R = Me; **b** R = cyclo-C_6H_{11}; **c** R = CH_2Ph; **d** R = Ph; **e** R = *p*-MeC_6H_4; **f** R = *p*-$MeOC_6H_4$; **g** R = *p*-ClC_6H_4; **h** R = *p*-BrC_6H_4

The investigations showed that compounds **4**, **6**, and **8** represent a new group of tautomeric systems with exceptionally interesting prototropic and acid–base characteristics. It was shown in the case of the 1,3-dimethyl derivatives **4b**,**d** and the 1,3-dimethyl-2-thio derivative **8c** that in aqueous solutions substances of this group are titrated as monobasic acids in the range of pH 0-14 without decomposition. According to independent data from pH-metry and spectrophotometry, for compound **4b** we obtained a pK_a value of 3.05, while for its 2-thio analog **8c** (spectrophotometric) we obtained 0.45. The acidity of the initial compounds **1b** (pK_a 4.72 [7]) and its 2-thio analog **7b** (pK_a 2.60 [8]) under these conditions is significantly lower. Thus, the introduction of a 4,5-dimethoxy-3-oxo-1,3-dihydro-1-isobenzofuranyl substituent into the active methylene group of barbituric acids leads to an increase of the acidity by approximately two orders of magnitude.



7 a R = H; **b** R = Me; **c** R = Et. **8 a, b** R = H; **c, d** R = Me; **e** R = Et; **a, b** R^1 = H; **c–e** R^1 = OMe

The obtained compounds **4** and **6** have a tautomeric structure and exist in solutions as a mixture of ketone (KET) and enol (EN) tautomers. Proton transfer in the EN–KET system in DMSO at room temperature proceeds quite slowly, and this makes it possible to observe the signals of the individual forms in the ^{1}H NMR spectra. As mentioned above, compounds **4b**,**d** in chloroform exist entirely in the ketone form, but in DMSO according to the spectra these substances are appreciably enolized. In the ^{1}H NMR spectra (DMSO-d_6) of compounds **4** and **6** there are broad peaks, and the signal of the mobile proton H-5 in the region of 4.50-4.88 ppm has reduced intensity, while two signals correspond to the H-1' proton: 5.99-6.36 (ketone) and 6.25-7.10 ppm (enol). From the ^{1}H NMR spectra we determined the quantitative content of the enolic forms, which for compounds **4** and **6** varies in the range from 25% for compound **4d** to 79% in the case of compound **6c** (Table 1). Compared with barbituric acid **1a**, which is enolized by only 2-3% in DMSO [5], 3-oxo-1,3-dihydro-1-isofuranyl derivatives of this series are distinguished by significantly greater enolizability in conjunction with increased acidity (see above). These results agree well with the familiar relation for *trans*-fixed β-diketones, according to which substituents that increase the CH acidity also increase the enolizability of the compound [7]. In line with this relation, according to data from the ^{1}H and ^{13}C NMR spectra, the 2-thio derivatives of this series **8a-e**, which have even higher acidity (see above), exist entirely in the enol form in solutions in DMSO.

Evidence for the existence of the enolic and not the ionized forms is provided by the identity of the ^{1}H NMR spectra of solutions of compounds **8a-e** in DMSO-d_6 and in a mixture of DMSO-d_6 and trifluoroacetic acid (5:1). We note that in the spectra of the enolic forms of compounds **8c**,**d** the protons signals of the N-methyl groups at positions 1 and 3 coincide, but in the ketone forms their signals differ appreciably, which is explained by the rapid, probably, intermolecular exchange between the two enolic forms EN–EN'.

In contrast to the solutions in DMSO, according to NMR spectroscopy, in chloroform compounds **4b,d** and their thio analogs **8c-e** only exist in the ketone form without any signs of enolization. The decrease in the content of the enolic tautomer in the transition from the polar solvating solvent DMSO to the low-polarity chloroform is quite regular [7], but it should be noted that the 2-thio derivatives **8c-e** change completely from the enolic form in DMSO to the ketone form in deuterochloroform. In comparison with the familiar tautomeric systems such a strong dependence of the position of equilibrium on the nature of the solvent can be called exceptional.

It can be concluded on the basis of the ^{1}H NMR spectra of compounds **8** that their ketone form is a mixture of two conformers differing in the mutual orientation of the H-5 and H-1' protons: *up-up* or *up-down*. In the spectra of compounds **8d**,**e** in deuterochloroform the H-1' proton in the region of 6.04-6.09 ppm corresponds to two signals of approximately equal intensity, one of which (a doublet, J = 2.2 Hz) probably belongs to the *up-down* isomer, while the second (a broad singlet with J < 1 Hz) corresponds to the *up-up* isomer. Isomerism of such a type is typical of natural compounds containing a lactonized fragment of opianic acid, e.g., for alkaloids of the narcotine group [9].

TABLE 3. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S (Hal)		
4a	$C_{12}H_8N_2O_5$	55.02 / 55.39	3.33 / 3.10	10.50 / 10.77		255	90
4b	$C_{14}H_{12}N_2O_5$	58.24 / 58.33	4.40 / 4.30	9.56 / 9.72		181	83
4c	$C_{14}H_{12}N_2O_7$	52.10 / 52.50	3.96 / 3.78	8.51 / 8.79		260	85
4d	$C_{16}H_{16}N_2O_7$	55.05 / 55.17	4.69 / 4.63	7.98 / 8.04		201	80
6a	$C_{15}H_{14}N_2O_7$	53.65 / 53.89	4.43 / 4.22	8.13 / 8.38		236	75
6b	$C_{20}H_{22}N_2O_7$	60.12 / 59.70	5.06 / 5.01	6.85 / 6.96		290	79
6c	$C_{21}H_{18}N_2O_7$	61.83 / 61.46	4.26 / 4.42	6.66 / 6.83		242	74
6d	$C_{20}H_{16}N_2O_7$	60.48 / 60.61	4.23 / 4.07	6.95 / 7.07		275	80
6e	$C_{21}H_{18}N_2O_7$	61.67 / 61.46	4.31 / 4.42	6.69 / 6.83		266	71
6f	$C_{21}H_{18}N_2O_8$	58.85 / 59.15	4.48 / 4.26	6.44 / 6.57		290	70
6g	$C_{20}H_{15}ClN_2O_7$	55.51 / 55.76	3.31 / 3.51	6.34 / 6.50	(8.01) / (8.23)	288	76
6h	$C_{20}H_{15}BrN_2O_7$	50.78 / 50.54	3.34 / 3.18	5.71 / 5.89	(16.40) / (16.81)	280	72
8a	$C_{12}H_8N_2O_4S$	46.35 / 46.75	2.90 / 2.62	8.83 / 9.09	10.29 / 10.40	>250	70
8b	$C_{14}H_{12}N_2O_6S$	49.64 / 50.00	3.81 / 3.60	8.15 / 8.33	9.47 / 9.53	>250	72
8c	$C_{14}H_{12}N_2O_4S$	50.12 / 50.59	3.96 / 3.64	6.22 / 8.43	9.50 / 9.65	154	65
8d	$C_{16}H_{16}N_2O_6S$	52.26 / 52.74	4.80 / 4.43	7.24 / 7.69	8.48 / 8.80	204	68
8e	$C_{18}H_{20}N_2O_6S$	55.17 / 55.09	5.25 / 5.14	6.99 / 7.14	8.12 / 8.17	136	55

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer at 500 MHz. The mass spectra were obtained on an MX-1303 instrument with direct injection into the ion source at 70 eV. The UV spectra were recorded on an SF-56 spectrophotometer for aqueous solutions (5×10^{-5} M); the pH of the aqueous solutions was measured on a pH 673 ionometer.

The acidity constants were calculated from the variation of the absorption of the solutions in the region of 260-280 nm [7], and the pK_a values were determined with an accuracy of up to 0.02. Thin-layer chromatography was conducted on Silufol UV-254 plates (chloroform–ethyl acetate, 3:1, and chloroform–ethyl acetate–formic acid, 10:5:1).

The N-substituted barbituric acids **5** were synthesized from the respective N-alkylureas and diethylmalonic ester [10].

5-(3'-Oxo-1',3'-dihydroisobenzofuran-1'-yl)barbituric Acid (4a). A sample of the acid **1a** (1.28 g, 0.01 mol) was dissolved by heating in 50% ethanol (20 ml), compound **2a** (1.65 g, 0.011 mol) was added, and the mixture was refluxed for 1 h. After cooling the precipitate was separated, washed with water and with ethanol, recrystallized from a mixture of ethanol and water, and dried over phosphorus pentoxide in a vacuum desiccator. We obtained 2.03 g of compound **4a**.

Compounds **4c**, **6a-h**, **8a**,**b** were obtained similarly.

1,3-Dimethyl-5-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)barbituric Acid (4b). To a mixture of the acid **1b** (1.56 g, 0.01 mol) and compound **2a** (1.56 g, 1.011 mol) we added carbon tetrachloride (20 ml). The mixture was refluxed for 3 h. After cooling the precipitate was separated, washed with carbon tetrachloride and then with hot water, dried, and recrystallized from carbon tetrachloride. We obtained 1.76 g of compound **4b**.

Compounds **4d**, **8c-e** were obtained similarly.

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