mg portion (1 mmole) of $NaBH_4$ is added to the filtrates, the mixture is held for 1 h at 20°C, neutralized by 30% AcOH, evaporated in vacuo to dryness, and evaporated with dry pyridine (3 × 10 ml). A 10 ml portion of dry pyridine and 5 ml of acetic anhydride are added to the residue, and the mixture is stirred for 16 h at 20°C. After the usual treatment and chromatography on silica gel, 0.3 g of nucleoside Va are obtained. R_f 0.25 (B). Subsequent deacetylation by an ammonia solution in methanol gives the nucleoside Vb. Yield 0.15 g (61%), mp 115-116°C (from alcohol). R_f 0.30 (C). UV spectrum, λ_{max} (ε), (pH 7): 268 nm (9500); (pH 13): 268 nm (7200). Found, %: C 49.0; H 6.5; N 11.2%. $C_{10}H_{16}N_2O_5$. Calculated, %: C 49.2; H 6.6; N 11.4.

1-[1,6-Dihydroxy-4-oxahex-3(S)-yl]thymine: 3',4'-seco-2'-desoxy-α-thymidine (VIb) was obtained in a similar way. Yield 70%. The scalar characteristics of nucleosides Va, b and VIa, b are identical. Found, %: C 49.0; H 6.4; N 11.1.

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SYNTHESIS, STRUCTURE, AND ACID–BASE CHARACTERISTICS OF ENAMINONES OF THE BARBITURIC ACID SERIES

D. V. Pestov, V. I. Slesarev, A. I. Ginak, and V. I. Slesareva

UDC 547.854.5:541.132.3:541.422.25

Enaminones were obtained by a tricomponent condensation of barbituric acids, aniline and triethyl orthoformate. The acid–base properties, PMR, UV and IR spectra of 5-anilinomethylene- and 1,3-dimethyl-5-anilinomethylenebarbituric acids are discussed. The properties of these compounds conform with a bipolar structure, in which the positive charge is distributed over the exocyclic part of the molecule, while the negative charge is distributed on the β-dicarbonyl fragment of the heterocyclic ring.

Interest in enaminones of the barbituric acid series arose because of their diverse biological activity [1, 2]. These compounds are formed in the reaction of barbituric acids with aniline and triethyl orthoformate [3, 4]. The reaction with an unsubstituted barbituric acid (Ia) was carried out in ethylene glycol at 140°C, and with 1,3-dimethylbarbituric acid (Ib), in boiling ethyl or butyl alcohols. The presence of water in the solvent strongly decreases the yield of the product. (See scheme on top of following page.)

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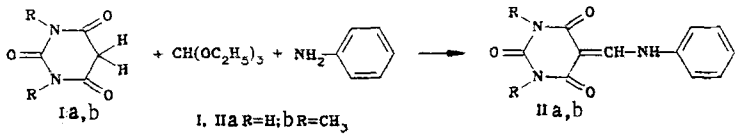
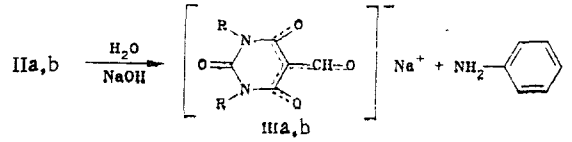


I. IIa R=H; b R=CH$_3$

Enaminones IIa,b formed have high melting points and low solubility in water and in most organic solvents, and in particular, 5-anilinomethylenebarbituric acid (IIa), are stable at 20°C in an acid medium, but are readily hydrolyzed in an alkaline medium to form aniline and salts of the corresponding 5-formylbarbituric acids (IIIa, b) [4].

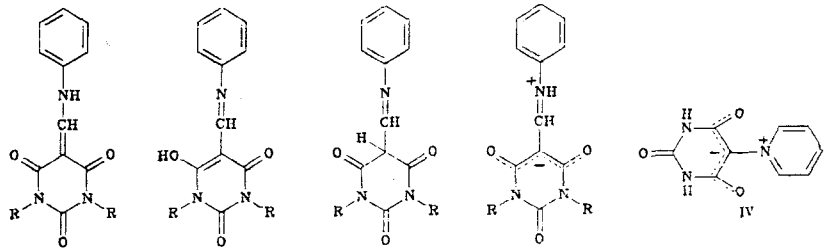


III a R=H; b R=CH$_3$

When 1,3-dimethyl-5-anilinomethylenebarbituric acid (IIb) is treated with sodium methylate in absolute methanol, its sodium salt is obtained, which is stable in the absence of water.

An enamine structure A is usually ascribed to enaminones of cyclic β-diketones, including derivatives of barbituric acids [5, 6]. Because of the absence in the IR spectra of IIb of bands characteristic of NH vibrations, the authors of [7] were able to represent these compounds as Schiff bases with structure B or C. Due to the presence in the molecules of these compounds of an exocyclic nitrogen atom with basic properties, on the one hand, and of a β-dicarbonyl fragment, tending not only to undergo keto–enol transformations, but also to form a stable ambidentate anion, on the other hand, a bipolar structure D can also be assumed for these compounds.

To clarify the structure of compounds IIa, b, we studied their acid–base properties, PMR, UV, and IR spectra. The similarity of the spectral characteristics and small differences in the acid–base properties of the compounds studied (Table 1) indicate that compounds IIa, b have one and the same structure.



IIa,b

Compounds IIa and IIb are totally protonated only in solutions of sulfuric acid at a concentration of more than 80%, while a proton is split off from compound IIb in an alkaline medium at pH > 11. Hence these compounds are very weak bases and weak acids. But, structures B and C presume that these compounds should be relatively strong acids, like 5-monosubstituted barbituric acids [8, 9]. Hence, these data indicate that structures B and C can be excluded for the compounds studied.

Analysis of PMR spectra of compounds IIa and IIb (Table 1), where signals of two protons in weak fields are observed in the 8.5 and 12 ppm region (doublets with the same SSCC J = 14 Hz) leads to the same conclusion. When a drop of D_2O is added to solutions of compounds studied in DMSO, because of exchange of the mobile hydrogen atoms for deuterium, the weak-field NH group proton signals (10-12 ppm) disappear in the PMR spectra, and signals in the 8.5 ppm region convert from a doublet into a singlet. In the PMR spectrum of the sodium salt of compound IIb, the signal of the CH_{exo} group is also singlet in character (Table 1). Thus, the PMR spectroscopic data indicate the presence in compounds IIa, b of an interaction between the NH and CH group protons, which is possible only in the case of structures A and D. The large chemical shift of the NH proton signal of the aniline fragment of the molecule (δ = 11.8 ppm) of compounds IIa, b indicates its participation in the intramolecular hydrogen bond, which intensifies due to the presence of a positive charge on the exocyclic nitrogen atom.

TABLE 1. Spectroscopic Characteristics and Acid-Base Properties of Compounds IIa, b

Compound	pK_{BH^+}	Form*	UV spectrum λmax, nm (ε)	PMR spectrum, ppm (J, Hz)†				
				medium	CH_3, s	CH_{exo}	NH_{exo}, d	C_6H_5, m
IIa	−3,6 ±0,2	N	223 (21900)‡; 340 (27900)	DMSO	—	8,50 d (J=14)	11,81 (J=14)	7,46
		C	215—225 plateau** (5380); 256 (7800); 341 (22400)	90% H_2SO_4	—	9,23 d (J=16)	12,6 (J=16)	7,90
IIb	−3,7 ±0,2 (pK_a 12,1± ±0,2)	N	224,5 (20700)‡; 343 (30600)	DMSO	3,21	8,62 d (J=14)	11,80 (J=14)	7,51
		C	234 (6800)‡; 260 (3500); 346 (22500)	90% H_2SO_4	3,55	8,99 d (J=16)	12,70 (J=16)	7,50
		A	261,5 (5825)††; 331 (21200)	DMSO‡‡	3,05	8,44 s	—	7,05

* N — neutral form, C — cation, A — anion.
† For the neutral form of compound IIa, the ring NH signal 10.88; 10.97 ppm, s.
‡ In methanol.
** In 90% H_2SO_4.
†† In methanol with addition of sodium methoxide.
‡‡ Spectrum of sodium salt of compound IIb.

The large SSCC of the CH and NH protons of the exocyclic groups indicates the multiplicity of the C=N bond in the substituent, and hence the presence of the $-CH=\overset{+}{N}H$ group, and not the =CH−NH− group in the molecule. The presence of a positively charged group in the molecule should exclude protonation of the compounds studied at the exocyclic fragment. In fact, in the PMR spectra of cations of compounds IIa and IIb in 90% sulfuric acid, there are no new signals, and only a regular shift of all the signals to the weak field is observed with retention of signals of doublets, characteristics of the $-CH=\overset{+}{N}H$ group (Table 1). These facts indicate that protonation of the compounds studied takes place not at the exocyclic group, but at the β-dicarbonyl fragment of the molecule, and only at the oxygen atoms. Hence, the PMR spectroscopy data on compounds IIa, b and their cations completely conform with the bipolar structure D.

Compared with the case of barbituric acids and their anions, in the UV spectra of the compounds studied an intense long-wave absorption band appears in the 340 nm region, indicating the presence of one single conjugation chain in the molecule between the hydroxypyrimidine ring and the substituent as a whole. The protonation and deprotonation of compounds IIa, b do not cause appreciable changes in the long-wave part of the UV spectrum, which indicates retention of the character of the conjugation chain in the neutral molecule, the anion, and cation of the compounds studied. In the UV spectra of the compounds studied, a high intensity long-wave band is retained, and a new band appears at 256-260 nm, which is characteristic of the monoenol form of barbituric acids. This also confirms the assumption on their protonation at the oxygen atoms of the β-dicarbonyl fragment.

The changes in the electronic spectra in the 225 nm region, depending on the concentration of sulfuric acid can be used to determine the protonation constants of 5-anilinomethylene-barbituric acids (Table 1). These valueswere found to be close to the protonation constants of 5-pyridinium-barbituric acid (IV) ($pK_{BH^+} = -2.6$). Its molecule is known to have a bipolar structure. According to the UV spectroscopy data, compound IV is protonated at the oxygen atoms of the β-dicarbonyl fragment (for the neutral molecule λ_{max} 248 nm, ε 19,950; for the cation λ_{max} 250 nm, ε 16,450).

Because of the rapid hydrolysis of the compounds studied in an alkaline medium, the UV spectra of the anion of compound IIb were taken in absolute methanol in the presence of sodium methoxide. Under these conditions, compound IIa can form a mixture of monoanions and a dianion, which hampers the interpretation of its UV spectrum in an alcoholic solution of sodium methoxide. By using the technique of rapid mixing of the reagents and recording the change

in the absorption band intensity at the analytical wave length (345 nm) in aqueous solutions with a fixed pH value, we succeeded to determine the acidity constant of compound IIb (Table 1). The weak acid properties of compound IIb conform well with structure D, in which the splitting of a proton is impeded because of the presence of a strong intramolecular hydrogen bond. During ionization of the compound in an alkaline medium, the stability of 5-anilinomethylenebarbituric acids in aqueous solutions sharply decreases. Thus, the acid–base properties and UV and PMR spectroscopy data on enaminones IIa, b are well explained, if it is assumed that in solutions these compounds have a bipolar structure D.

The IR spectroscopy data for solutions of compound IIb in DMSO and in chloroform agree with this conclusion. The IR spectra of compound IIb in the region of stretching vibrations of multiple bonds differ from the spectra of 1,3-dimethyl-5-benzylidenebarbituric acid, considered as a model of structure A, by a 20-40 cm^{-1} shift of the absorption band of the C=O bond to the low-frequency region, and are similar to the spectra of 1,3-dimethyl-5-pyridiniumbarbituric acid and the sodium salt of 1,3-dimethyl-5-anilinomethylenebarbituric acid, containing a $(O\cdots C\cdots C\cdots C\cdots O)^-$ anionic fragment. The 1720 cm^{-1} band, observed in the spectra of compound IIb is due to the stretching vibrations of the carbonyl group at the second position, the 1655-1635 cm^{-1} band is due to the vibrations of the C···O and C···C conjugated bonds of the anionic fragment of the molecule, while the bands at 1660-1585 and 1475-1450 cm^{-1} are caused by the phenyl ring vibrations. Assignment of the bands in the IR spectra of the compounds studied was based on their comparison with the spectra of the above model compounds, the spectra of aniline and its hydrochloride. Comparison of the spectra of compound IIb with the spectra of its deuterated derivative showed that there was a bond at 1660 cm^{-1}, characteristic of compounds containing an immonium group $C=\overset{+}{N}H$ [10], which in the spectra of a deuterated sample is shifted to 1540 cm^{-1}. This band is absent also in the spectra of the sodium salt of compound IIb. The IR spectra of the crystalline samples of compounds of IIa, b are similar to one another, as well as to the spectra of solutions of compound IIb. In these spectra bands are observed, which are characteristic of the anionic fragment (1655-1625 cm^{-1}), the $-CH=\overset{+}{N}H$ group (1670-1660 cm^{-1}), and the phenyl ring (1595-1573 and 1480-1440 cm^{-1}). Hence, enaminones IIa, b have a bipolar structure in both solutions and in crystalline state, in which the positive charge is distributed over atoms of the anilinomethylene substituent, while the negative charge is distributed over the atoms of the β-dicarbonyl fragment of the heterocyclic ring.

EXPERIMENTAL

The electronic spectra were run on SF-20 and SF-26 spectrophotometers at a 10^{-5} M concentration of the solutions, the IR spectra on an IKS-29 spectrophotometer in a suspension in a perfluorinated mineral oil, in solutions in chloroform and in DMSO, at a layer thickness of 0.6 mm. The PMR spectra were obtained on RYa-2309 (90 MHz) and RYa-2310 (60 MHz) spectrometers using HMDS as internal standard and 90% H_2SO_4 as external standard.

The acid ionization constant of compound IIb was determined spectrophotometrically. A 1 ml portion of a buffer solution or a titrated KOH solution was added to 2 ml of an aqueous solution of compound IIb in a quartz cuvette, 1 cm thick, and the optical density of the mixture obtained was immediately recorded at 345 nm. The time from the moment of mixing the reagents to the beginning of recording was less than 1 sec, which did not exceed 5% of the half-conversion time of the compound studied during hydrolysis. From these measurements, the optical density of solutions containing a mixture of the two acid–base forms and a pure anion of compound IIb were determined, and also the acid ionization constant of this compound was calculated.

Protonation of compounds IIa, b and IV was studied spectrophotometrically in sulfuric acid solutions. In the calculations of protonation constants, the acidity function was used describing the protonation of amines H_A, since the protonation of compounds IIa, b and IV was described best only by this acidity function.

5-Anilinomethylenebarbituric Acid (IIa). A 25.6 g portion (0.2 mole) of barbituric acid was dissolved at 100°C in 500 ml of ethylene glycol, 18.2 ml (0.2 mole) of aniline and 36.6 ml (0.22 mole) of triethyl orthoformate were added. The temperature was raised to 140°C and the mixture was held at this temperature for 30 min. It was then cooled to 70°C, the precipitate was filtered, washed with hot ethylene glycol and acetone, and dried. The product was recrystallized from DMFA. Yield 39.1 g (84.7%), mp > 300°C. Found, %: C 56.6; H 4.2; N 18.4. $C_{11}H_9N_3O_3$. Calculated, %: C 57.1; H 4.0; N 18.2.

1,3-Dimethyl-5-anilinomethylenebarbituric Acid (IIb) was obtained in a similar way. The reaction was carried out in boiling butanol. Yield 91%, mp 198-199°C (ethanol). Found, %: C 60.2; H 5.0; N 16.4. $C_{13}H_{13}N_3O_3$. Calculated, %: C 60.2; H 5.1; N 16.2.

Sodium Salt of 1,3-Dimethyl-5-anilinomethylenebarbituric Acid. A 5.5 ml portion of a 2 M solution of sodium methoxide (0.011 mole) in absolute methanol was added at 20°C to 2.59 g (0.01 mole) of 1,3-dimethyl-5-anilinomethylenebarbituric acid. The suspension obtained was stirred for 30 min, the precipitate was filtered, washed with methanol, and dried in vacuo. The yield was practically quantitative.

5-Pyridinium-barbituric Acid (IV) was obtained by a method described in [11].

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SYNTHESIS AND STUDY OF STRUCTURE OF 5-FORMYL-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

N. A. Puodzhyunaite, R. A. Yanchene, and Z. A. Stumbryavichyute

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A series of 5-formyl derivatives was synthesized by formylation of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones with a mixture of formic acid and acetic anhydride. The structure of their rotation isomers was studied by PMR spectroscopy.

The restrained internal rotation around the noncyclic N—C bond in N-acylindolines and N-acyltetrahydroquinolines was studied by several groups of authors [1-3]. For the derivatives of seven-membered saturated nitrogen-containing heterocyclic compounds, this process has practically not been investigated.

The present work was devoted to the synthesis of 5-formyl derivatives of the 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones of the general formula I-XII and the study of their rotation isomerism by PMR spectroscopy. (See scheme on following page.)

In the first experiments, the 5-formyl derivatives I, II were obtained by reacting tetrahydrobenzodiazepinones XIII, XIV with 85% formic acid in benzene [4], in yields not exceeding 30%, and the amount of unreacted starting compounds reached 50%. Later, a mixture of 98% formic acid and acetic anhydride was used for the formulation. By carrying out the process at room temperature, the possible participation in the reaction of acetic anhydride

Institute of Biochemistry, Academy of Sciences of the Lithuanian SSR, Vil'nyus 232021.

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