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Tetracarbonyl Systems: VII.* Reactions of 1,3,4,6-Tetracarbonyl Compounds with *o*-Aminothiophenol in the Synthesis of Regioisomeric 3(2)-Aroylmethylene-1,4-benzothiazin-2(3)ones

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Abstract—In reaction of 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones with *o*-aminothiophenol (3*Z*)-3-aroylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-ones were obtained in a preparative yield. In solution of the latter compounds an enamine-imine tautomerism was observed. In reaction of ethyl esters or amides of 2-substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acids with the *o*-aminothiophenol regioisomeric 2-aroylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-ones were formed.

Heterocyclic derivatives of 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones (**I**: tautomeric forms A, B, and C) forming at their dehydration 5-aryl-2-aroylmethylene-2,3-dihydrofuran-3-ones (**II**) [2–4] are known to readily react with *o*-aminothiophenol affording biologically active 2,3-bisaroylmethylene-2,3-dihydro-4*H*-1,4-benzothiazines (**III**) (Scheme 1) [4–6].

Attempts to obtain benzothiazines **III** by direct reaction of tetraketones **I** with the *o*-aminothiophenol failed [4, 6]. In reaction of compounds **Ia, b** with the latter reagent under relatively mild conditions (short heating in acetic acid) we isolated with a preparative yield (3*Z*)-3-aroylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-ones (**IVa, b**: tautomers D and E) (Scheme 1).

Note that apart from our preliminary communications [7–9] no published data exist on reaction with the *o*-aminophenol of tetracarbonyl systems containing simultaneously α and β dioxo fragments.

In the course of detailed investigation of reactions between tetracarbonyl compounds and *o*-aminophenol we also established that at treatment with this reagent of ethyl esters or amides of 2-substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acids **Va–c** arose regioisomeric compounds 2-aroylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-ones (**VIa, b**) (Scheme 2).

It should be noted that 3(2)-acylmethylene derivatives of 1,4-benzothiazin-2(3)ones are poorly known and almost not studied. For instance, a synthesis was reported of 3-pentafluorobenzoylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-one (**IVc**) by treating a copper salt of methyl pentafluorobenzoylpyruvate with *o*-aminothiophenol hydrochloride [10] (Scheme 2).

An *o*-hydroxyphenylamide of 2,4-dioxo-3-(3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-2-ylidene)-4-*p*-tolylbutanoic acid (**VII**) was also prepared by reaction of 3-*p*-toluoyl-1,2-dihydro-4*H*-pyrrolo[5,1-*c*][1,4]-benzoxazine-1,2,4-trione with *o*-aminothiophenol [11]. Prior to our studies [7–9, 12–14] no other acylmethylene derivatives of 1,4-benzothiazines were known. Therefore we should point out that the data on the synthesis of 2-aroylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-ones **VI** by reaction of aroylpyruvic acids or 5-aryl-2,3-dihydrofuran-2,3-diones with *o*-aminothiophenol [15–18] are not reliable. According to our data these reactions gave rise only to precursors of thiazines **VI**, 4-aryl-2-*o*-mercaptophenylamino-4-oxo-2-butenoic acids **VIII**, and to cyclic O,S-acetals, 2-aroylmethyl-2-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-ones **IX**, and under more stringent conditions 1,4-benzothiazin-2,3-dione (**X**) was isolated [7, 8, 12, 13]. We also established that 2-dibenzoylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-one **XI** resulted from the reaction between 4-benzoyl-5-phenyl-2,3-dihydrofuran-2,3-dione and *o*-aminophenol [7, 8, 12–14] (Scheme 2).

Compounds synthesized **IVa, b** and **VIa, b** are yellow crystalline substances insoluble in water, sparingly soluble in ethanol, ethyl acetate, and soluble in DMSO.

Spectral parameters of (3*Z*)-3-aroylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-ones (**IV**) are con-

* For communication VI see [1].

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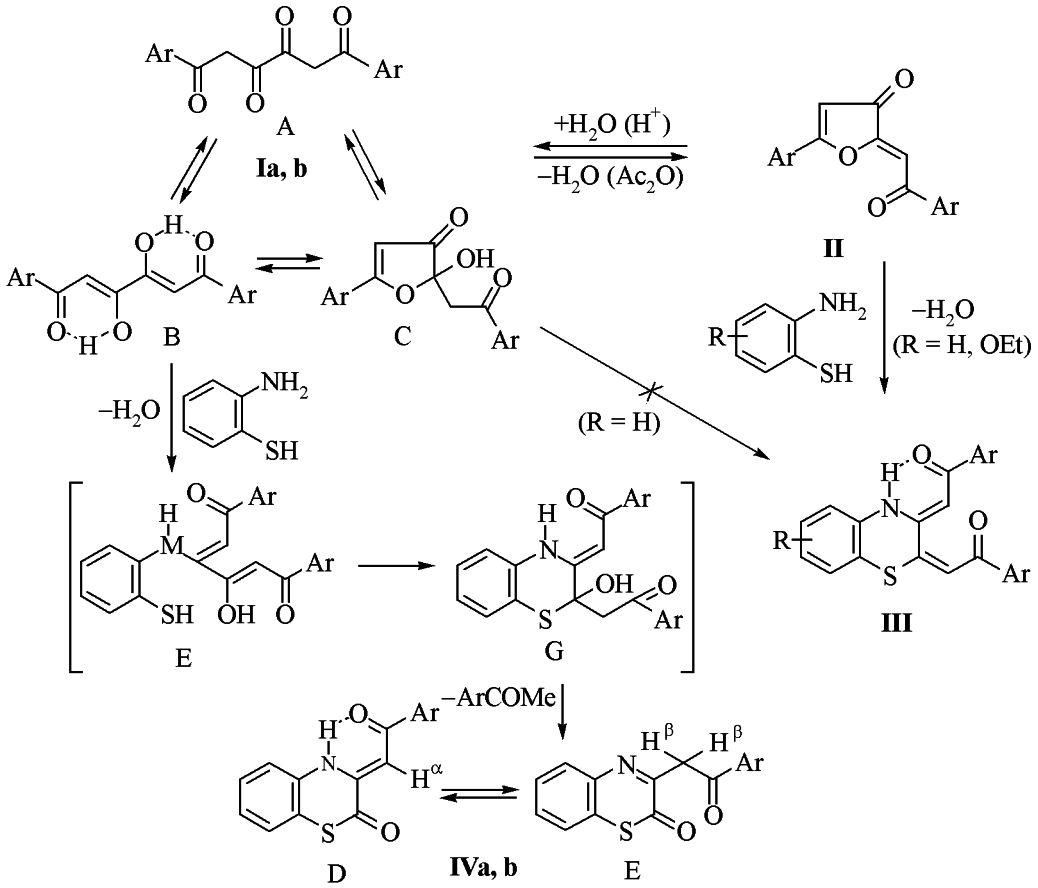
Scheme 1.



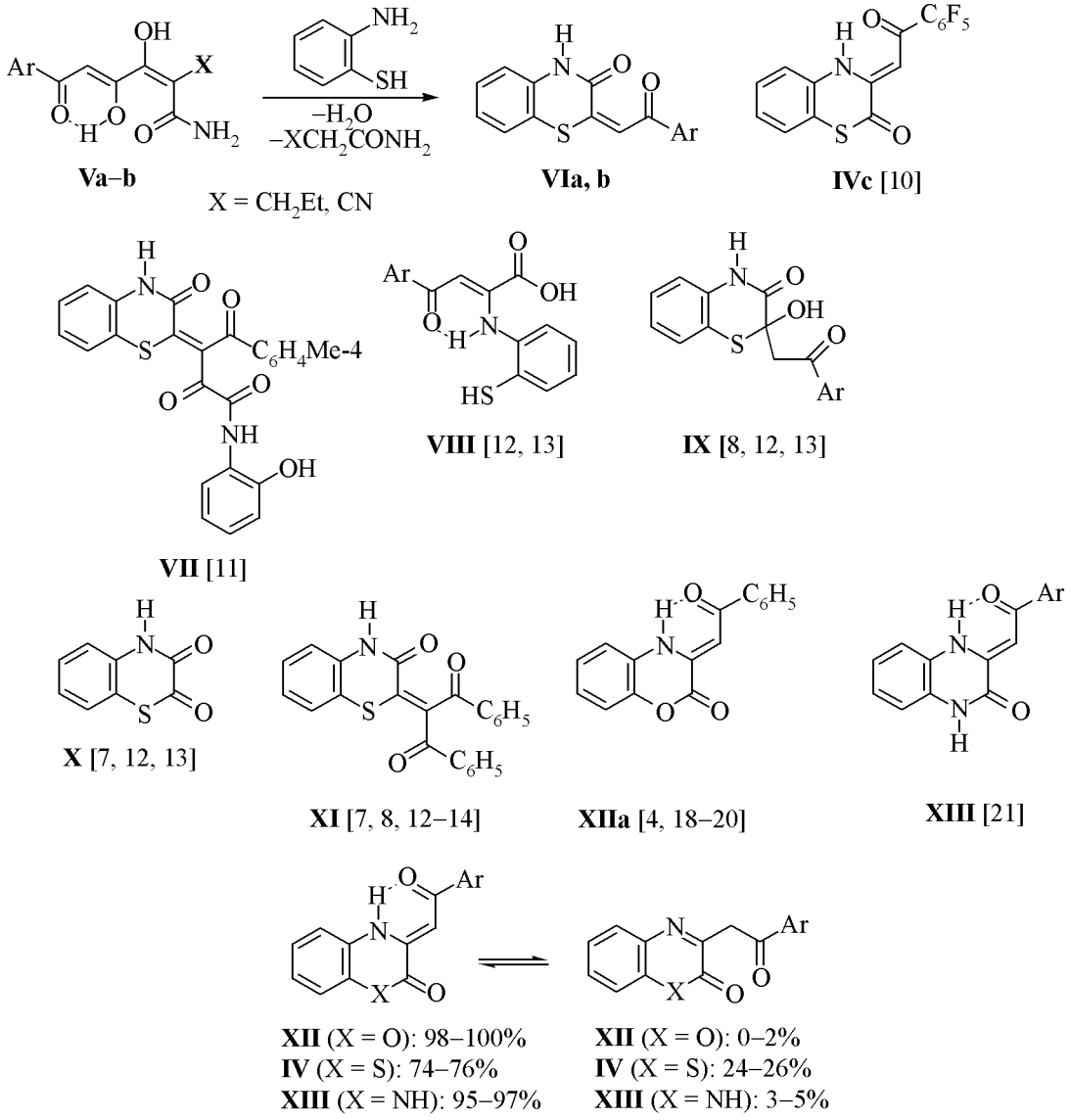
Ar = C_6H_5 (**Ia, IVa**), 4-$CH_3C_6H_4$ (**Ib, IVb**).

sistent with their assumed structure. We compared these data with spectral characteristics of a known and similar in structure (3*Z*)-3-benzoylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (**XIIa**) [4, 18–20]. The spectra of the regioisomeric 2-aroylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-ones (**VIa, b**) also are in good agreement with their assumed structure.

In the crystalline state compounds **IV** exist in the enamine structure **IVd** containing NH-chelate fragment with an intramolecular hydrogen bond of the type –N–H··· O=C< [21]. It is evidenced in particular by the presence in the 1,4-benzothiazine **IVa** IR spectrum of a broad low-frequency band corresponding to the stretching vibrations of the carbonyl group from the conjugated aroyl unit of the NH-chelate at 1590–1630 cm^{-1}. In this range occur also the low-frequency stretching vibrations of the carbonyl C^2=O from thiolactone in agreement with the well-known data [22]. Note for comparison that in the IR spectrum of 1,4-benzoxazine **XIIa** the absorption band of the NH-chelate appears in a similar frequency range, at 1590–1602 cm^{-1}, and the stretching vibrations of the carbonyl C^2=O from lactone are located at considerably higher frequencies, at 1754 cm^{-1}, and this is also consistent with the classical data [22]. In the IR spectrum of 1,4-benzothiazin-3(4*H*)-one **VIa** regioisomeric to compound **IVa** are present the characteristic bands of stretching vibrations of amide group NH from lactam unit at 3228 cm^{-1} and of carbonyl from this amide group at 1668 cm^{-1}, and also the band of stretching vibrations of carbonyl group from the conjugated benzoyl fragment at 1616 cm^{-1}; these data support the assumed structure of compound **VIa**.

In the ^{1}H NMR spectra of 1,4-benzothiazines **IVa, b** recorded in DMSO-d_6 a presence of two equilibrium tautomers was revealed: the prevailing enamine (**IVD**, respective content 74 and 76%) with characteristic signals of methine proton CH^{α} at 7.41 and 7.48 ppm, and imine (**IV E**, respective content 26 and 24%) characterized by singlets from two protons of CH_2^{β} group at 4.92 and 5.06 ppm respectively. The N^4H group proton did not appear in the spectra, and in the published data on the spectrum of the

Scheme 2.



Ar = C_6H_5 (**Va, Vc, VIa**), 4-$CH_3C_6H_4$ (**Vb, VIb**); X = CO_2Et (**Va, Vb**), C≡N (**Vc**).

fluorine-containing analogous compound **IVc** the signal of the amino group of the ring was mentioned as diffuse downfield resonance at 13.6 ppm [10]. The characteristic signal of the methine CH^{α} proton in the spectra of the enamine form of compounds **IV** is shifted downfield by 0.5 ppm as compared with the corresponding signal in compound **XIIa** (6.91 ppm) due to stronger shielding from sulfur than oxygen atom in the heterocycle. Therewith it should be noted that unlike 1,4-benzothiazines **IV** in solutions of (3*Z*)-3-aroylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-ones (**XII**) the imine form in the ring ($C^3=N^4$) is lacking [4, 20, 23] or appears in a negligible amount, from fractions of percent to 1–2% in acid medium [23, 24]. At the same time in the ^1H NMR spectra of similar in structure (3*Z*)-3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones (**XIII**) also registered in DMSO-d_6 the imine tautomer was observed in considerable amount (3–5%) [21]. Thus in going from 2-oxo derivatives of 1,4-benzoxazine **XII** through quinoxalin-2-ones **XIII** to 1,4-benzothiazin-2-ones **IV** the equilibrium amount of imine form in solution significantly grows (Scheme 2).

Note also that at addition to the solution of compounds **IVa, b** in DMSO-d_6 of trifluoroacetic acid the positions of proton signals in the spectra almost did not change, and the content of tautomers **IV D** and **IVE** also remained the same as before.

The signal of methine CH proton in the H^1 NMR spectra of 1,4-benzothiazines **VIa, b** taken in DMSO-d_6 solution (δ 8.23 and 8.24 ppm respectively) is located downfield (by 0.8 ppm on the average) from the corresponding signal in the spectra of compounds **IV** and thus is a distinguishing characteristic. Besides the spectra of compounds **VIa, b** contain characteristic signals of amide proton N^4H of the ring at δ 11.60 and 11.62 respectively; this signal is lacking in the spectra of 1,4-benzothiazines **IV**. Regretfully, no comparable compounds as were chosen for 1,4-benzothiazines **IV** were known for derivatives **VI**: 2-aroylmethylene-3,4-dihydro-2*H*-1,4-benzoxazines did not exist.

It should be noted in connection with interpretation of the ^1H NMR spectra that at the synthesis of 1,4-benzothiazines **IV** and **VI** a thorough purification of crude products is required from the impurities of the initial 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones (**Ia, b**) or ethyl esters or amides of 2-substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acids (**Va–c**): The initial compounds tend to crystallize together with products. The purity of compounds **IV** is checked by the lack of the characteristic signal of coupled geminal protons of CH_2 group belonging to the ring 3-oxofuran form **I C** of the initial 1,3,4,6-tetraketones in the ^1H NMR spectra registered in DMSO-d_6. For instance, the corresponding impurity of the initial compound **Ia** (ring form **I C**, 53%) is identified by two doublets at 3.48 and 3.95 ppm, $J\ CH_2^{gem}$ 14.0 Hz [25]. The purity of compounds **VI** is checked by the lack of characteristic ethyl group signals from the ester fragment of compounds **Va, b** at 1.22–1.24 ppm (t) and 4.18–4.20 ppm (q), or by the lack of signals from the amide group protons of compound **Vc** located upfield (8.83–10.33 ppm) from the signal of the N^4H group in the ring of products **VIa, b** [1].

The fragmentation of regioisomeric 1,4-benzothiazines **IV** and **VI** under the electron impact occurs as expected with ejection of aroyl and aroylmethylene fragments to form relatively stable ions with a core of oxobenzothiazines. Unexpectedly decomposition of compounds **IV** and **V** involves the decarbonylation of molecular ions to afford relatively abundant (15–51%) ions $[M–CO]^+$. The peaks of molecular ions in the mass spectra of compound **IV** and **VI** are also of considerable intensity (34–84%) evidencing their relative stability against the electron impact.

The formation of 1,4-benzothiazines **IV** is likely to originate from the primary nucleophilic attack of the amino group of *o*-aminophenol at the C^3 (or C^4 with equal probability) in the dienol form of 1,3,4,6-tetraketones **I** affording intermediates **F** or **G** followed by hydrolytic cleavage of aryl methyl ketones from the intermediate cyclic O,S-acetal **G** (Scheme 1). In a similar way may occur attack of the most electrophilic site C^3 in substrates **V** with subsequent heterocyclization and elimination of ethyl malonamide or respectively cyanoacetamide furnishing regioisomeric compounds **VI**.

Obtained compounds **IV** and **VI** exhibit bacteriostatic activity with respect to strains *Staphylococcus aureus* P-209 and *Escherichia coli* M_{17} [8, 26]; therewith the regioisomer **IVa** is highly active.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 from mulls in mineral oil. ^1H NMR spectra were registered on spectrometers Bruker AC-300 (300.13 MHz) and Bruker DRX-500 (500.13 MHz) from solutions in DMSO-d_6, internal reference TMS. Mass spectra were measured on Kratos MS-30 instrument (Great Britain) with direct admission of the sample into the ion source (electron impact), emission current 1000 mA, ionizing voltage 70eV, vaporizer temperature 100–150°C.

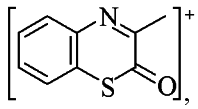
The homogeneity of compounds was proved by TLC on Silufol UV-354 plates in a system benzene–ethyl ether–acetone (10 : 9 : 1), development in iodine vapor.

The initial 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones (**Ia, b**) were obtained by Claisen condensation of the appropriate aryl methyl ketones with diethyl oxalate in the presence of sodium methylate [25]. Ethyl esters and amides of 2-substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acids (**Va–c**) were prepared by procedure [1]. (3*Z*)-3-Benzoylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (**XIIa**) was obtained by reaction between 3,4-dihydroxy-1,6-diphenyl-2,4-hexadiene-1,6-dione (**Ia**) with *o*-aminophenol [20].

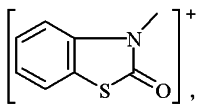
(3*Z*)-3-Aroylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-ones (IVa, b). A mixture of 2 mmol of an appropriate 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-dione (**Ia, b**) and 0.25 g (2 mmol) of *o*-aminothiophenol was heated at stirring in 10–20 ml of acetic acid till dissolution of reagents, then the reaction mixture was boiled for 1–3 min (TLC monitoring). After 3–5 h the separated precipitate was filtered off and recrystallized from ethanol. The obtained target compounds **IVa, b** are yellow crystalline substances.

(3*Z*)-3-Benzoylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-one (IVa). Yield 0.40 g (71%), mp

154–155°C. IR spectrum, ν, cm^{-1}: 1590–1630 ($C^2=O$, C_6H_5CO in NH-chelate), 1582, 1560, 1540, 1460, 1378, 1300. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.06 s [2H, CH_2^{β}, imine (**IV E**), 26%], 7.48 s [1H, CH^{α}, enamine (**IV D**), 74%], 7.57–7.70 and 8.03–8.28 m (9H, C_6H_5, C_6H_4). Proton signal from N^4H group lacks in the spectrum (in the spectrum of **IVc** analog is present a diffuse downfield signal at 13.6 ppm [10]). Mass spectrum, *m/z* (I_{rel}, %), ion peaks with I > 5% are listed: 282 (7) $[M+H]^+$, 281 (34) $[M]^+$, 253 (20) $[M-CO]^+$, 252 (13) $[M-CO-H]^+$, 236 (7), 162 (10) $[M-C_6H_5COCH_2]^+$ or

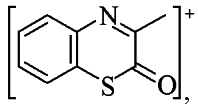


150 (14) $[C_7H_4NOS]^+$ or

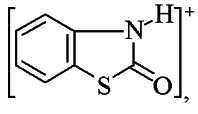


147 (14), 136 (7), 135 (26), 134 (11), 131 (11), 108 (10), 106 (8), 105 (100) $[C_6H_5-C\equiv O]^+$, 102 (36), 77 (56) $[C_6H_5]^+$, 75 (5), 69 (46), 65 (5). Found, %: C 68.62; H 4.25; N 5.17. $C_{16}H_{11}NO_2S$. Calculated, %: C 68.31; H 3.94; N 4.98.

(3*Z*)-3-*p*-Methylbenzoylmethylene-3,4-dihydro-2*H*-1,4-benzothiazin-2-one (IVb). Yield 0.38 g (64%), mp 144–145°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.46 s [3H, CH_3, enamine (**IV D**), 76%], 2.52 s [3H, CH_3, imine- (**IV E**), 24%], 4.92 s [2H, CH_2^{β}, (IV E)], 7.41 s [1H, CH^{α}, (IV D)], 7.36, 7.58–7.63 and 7.97–8.17 m (8H, $2C_6H_4$). Proton of signal from N^4H group lacks in the spectrum. Mass spectrum, *m/z* (I_{rel}, %), ion peaks with *I* > 5% are listed: 296 (11) $[M+H]^+$, 295 (62) $[M]^+$, 267 (15) $[M-CO]^+$, 266 (18) $[M-CO-H]^+$, 250 (11), 162 (18) $[M-4\text{-}CH_3C_6H_4COCH_2]^+$ or



161 (22), 151 (57) $[C_7H_5NOS]^+$ or



136 (9), 135 (24), 134 (21) $[4\text{-}CH_3C_6H_4COCH_3]^+$, 120 (6), 119 (67) $[4\text{-}CH_3C_6H_4C\equiv O]^+$, 117 (11), 116 (100) $[4\text{-}CH_3C_6H_4C\equiv CH]^+$, 108 (11), 91 (39) $[4\text{-}CH_3C_6H_4]^+$, 77 (9), 69 (58), 65 (18). Found, %: C 68.85; H 4.63; N 4.59. $C_{17}H_{13}NO_2S$. Calculated, %: C 69.13; H 4.44; N 4.74.

2-Aroylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-ones (VIa, b). A mixture of 5.0 mmol of an appropriate ethyl 6-aryl-3,4-dihydroxy-2-carbamoyl-6-oxo-2,4-hexadienoate (**Va, b**) or 1.29 g (5.0 mmol) of 3,4-dihydroxy-6-oxo-6-phenyl-2-cyano-2,4-hexadienoic acid amide (**Vc**) and 0.63 g (5 mmol) of *o*-aminothiophenol was heated at stirring in 30–50 ml of acetic acid till dissolution of reagents, then the reaction mixture was boiled for 1–3 min [procedure (a)] or heated at stirring in 80–100 ml of ethanol till dissolution of reagents and then heated at reflux for 2–3 h (procedure (b) (TLC monitoring). After 5–7 h the separated precipitate was filtered off and recrystallized from dioxane. The obtained target compounds **VIa, b** are yellow crystalline substances.

2-Benzoylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-one (VIa). Yield 0.51 g (36%) [procedure (a)], from compound **Va**), 0.90 g (64%) [procedure (b)], from compound Va), 0.76 g (54%) [procedure (b)], from compound **Vc**), mp 279–280°C. IR spectrum, ν, cm^{-1}: 3228 (CONH), 1668 (CONH), 1616 ($C_6H_5COCH=$), 1592, 1576, 1532, 1504, 1460, 1378, 1256, 1232. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.12–7.31, 7.47–7.65 and 8.03 m (9H, C_6H_5, C_6H_4), 8.23 s (1H, CHCOPh), 11.62 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %), ion peaks with *I* > 5% are listed: 282 (8) $[M+H]^+$, 281 (37) $[M]^+$, 254 (5), 253 (29) $[M-CO]^+$, 252 (26) $[M-CO-H]^+$, 220 (7), 204 (16) $[M-C_6H_5]^+$ $o, 176 (26) $[M-C_6H_5CO]^+$, 147 (15), 131 (11), 129 (9), 127 (8), 121 (7), 106 (7), 105 (80) $[C_6H_5-C\equiv O]^+$, 104 (9), 96 (5), 90 (6), 89 (6), 78 (11), 77 (100) $[C_6H_5]^+$, 76 (7), 69 (12), 65 (6). Found, %: C 68.15; H 3.87; N 4.91. $C_{16}H_{11}NO_2S$. Calculated, %: C 68.31; H 3.94; N 4.98.

2-*p*-Methylbenzoylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-one (VIb). Yield 0.47 g (32%) (procedure *a*, from compound **Vb**), 0.71 g (48%) (procedure *b*, from compound **Vb**), mp 267–268°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.41 s (3H, CH_3), 7.12 t, 7.18 d, 7.29 t, 7.38 d, 7.48 d, 7.92 d (8H, 2 C_6H_4), 8.24 s (1H, CHCOC$_6$H$_4$CH$_3$-4), 11.60 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %), ion peaks with *I* > 5% are listed: 297 (6) $[M+2H]^+$, 296 (14) $[M+H]^+$, 295 (84) $[M]^+$, 268 (11), 267 (51) $[M-CO]^+$, 266 (72) $[M-CO-H]^+$, 252 (5) $[M-CO-CH_3]^+$, 250 (5) $[M-CO-CH_3-H]^+$, 234 (20), 204 (12) $[M-C_6H_4CH_3\text{-}4]^+$, 176 (18) $[M-4\text{-}CH_3C_6H_4CO]^+$, 175 (14), 148 (15), 143 (6), 134 (7), 133 (10), 126 (15), 121 (5), 120 (7), 119 (59) $[4\text{-}CH_3C_6H_4C\equiv O]^+$, 104 (5), 92 (7)=, 91 (100) $[4\text{-}CH_3C_6H_4]^+$, 89 (13), 77 (9), 69 (6), 65 (45). Found, %: C 69.32; H 4.22; N 4.91. $C_{17}H_{13}NO_2S$. Calculated, %: C 69.13; H 4.44; N 4.74.

(3*Z*)-3-benzoylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (XIIa) [4, 18–20]. IR spectrum, ν, cm^{-1}: 1754 (C^2=O lactone), 1590–1602 (C_6H_5CO in NH-chelate). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.91 s (1H, CHCOPh), 7.13–7.24, 7.55, 8.03 m (9H, C_6H_5, C_6H_4), 12.86 s (1H, NH).

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