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Synthesis of Endocyclic Enol Methyl Ethers of 3-Acylthiotetronic Acids and Their Reactions with Amines

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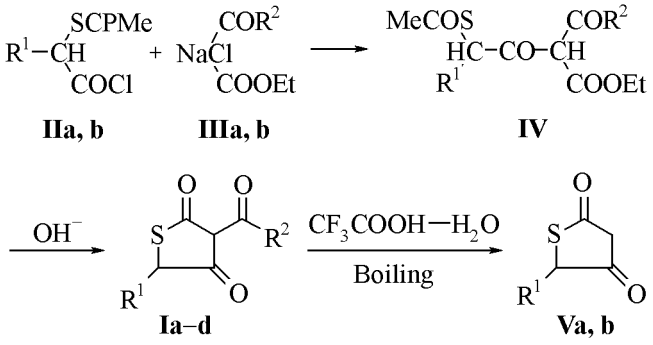
Abstract—Acylation of (3*H*,5*H*)-tetrahydrothiophene-2,4-dione (thiotetronic acid) with acetyl, propionyl, and valeryl chlorides followed by O–C isomerization in the presence of 4-dimethylaminopyridine or acetone cyanohydrin gave rise to 3-acetyl, 3-propanoyl, and 3-pentanoyl derivatives of thiotetronic acid. The reaction of 3-acylthiotetronic acids with diazomethane afforded enol methyl ethers at the endocyclic keto groups. The subsequent reaction of these enol ethers with allylamine, benzylamine, and *p*-anisidine occurs along the mechanism of vinylog substitution providing the corresponding endocyclic enamino derivatives.

Unlike widely spread in nature and already thoroughly studied tetronic [1] and tetramic [2] acids and their versatile synthetic derivatives the interest to the chemistry and biological activity of (3*H*,5*H*)-tetrahydrothiophene-2,4-dione (thiotetronic acid) derivatives is not so pronounced. The 3-acyl derivatives of the thiotetronic acid that attracted our attention are no exclusion in this respect. Among compounds of this series were found substances with immunosuppressive [3], antiphlogistic [4], herbicide [5] properties. Enamino derivatives at exocyclic carbonyl group of 3-acetylthiotetronic acid showed antitumor activity [6]. Since we found no publications on synthesis and biological activity of enamino derivatives at endocyclic keto groups of 3-acylthiotetronic acids and since no general and efficient procedures existed for introduction of acyl substituents into the *3* position of the tetrahydrothiophene-2,4-dione we undertook an attempt to solve these problems basing on our experience in the field of the chemistry of 2-acylcycloalkane-1,3-diones [7].

The described procedure [3, 8] for preparation of 3-acetylthiotetronic acid (**Ia**) and 3-ethoxycarbonylthiotetronic acid (**Ib**) consisted in reaction of chloride of *S*-acetylthioglycolic acid (**IIa**) with sodium salts of the corresponding ethyl acetoacetate (**IIIa**) or diethyl malonate (**IIIb**) followed by cyclization of intermediate compound **IV** under alkaline conditions. This method turned out to be well reproducible, simple and efficient way of building up the ring of the 2,4-tetrahydrothiophenedione.



R^1 = H (**a**), Me (**b**–**d**); R^2 = Me (**a, c**), OEt (**b, d**).

The decarboxylation of diketo ester **Ib** occurred under mild conditions and furnished in 70% yield thiotetronic acid (**Va**) identical in physical properties to the described compound [3, 8]. Using in the above procedure S-acetyl-2-mercapotopropionyl chloride (**IIb**) we succeeded in preparation of 5-methyl derivatives of thiotetronic acid **Ic** (yield 18%) and **Id** (yield 65%). Decarboxylation of the latter substance in 70% trifluoroacetic acid afforded 5-methylthiotetronic acid (**Vb**) with the same physical characteristics as the compound described in [9].

Acylation of diketones **Va, b** with acetyl chloride in the presence of triethylamine gave rise to mixtures of O-acyl derivatives at different keto groups of the dicarbonyl system f the 2,4-thiophenedione in agreement with the published data [3]. The obtained mixtures of enol acylates were without isolation subjected to isomerization into 3-acetyl derivatives by treating with 4-dimethylaminopyridine or acetone cyanohydrin. These catalysts we previously applied to the synthesis of β-triketones of cyclohexane series [10]. At the use of both catalysts the target compounds **Ia, c** were isolated in 40–45% yield (Table 1). The compounds were identical to the samples we had obtained by the above mentioned procedure. By applying propionyl and valeryl chlorides for acylation of diketones **Va, b** we obtained 3-propanoyl and

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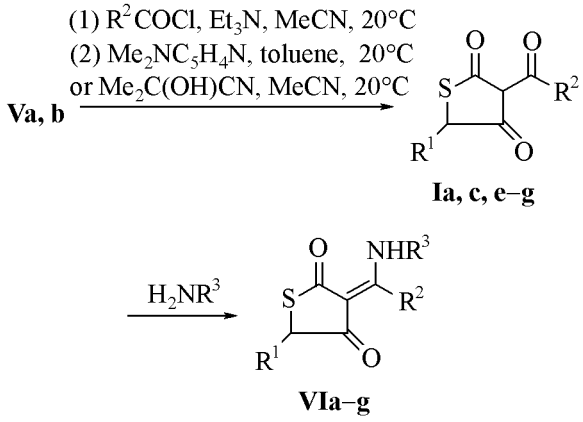
Table 1. Yields, melting points, and elemental analyses of 3-acylthiotetronic acids **Ia, c, e–g** obtained by acylation, and endocyclic methyl ethers **VIIa, VIIIa**

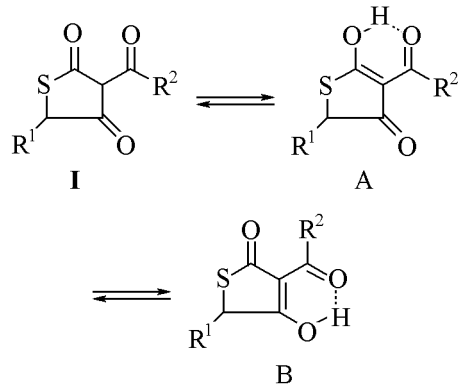
Compd. no.	Yield, % (method)	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	S		C	H	S
Ia	45 (*a*), 40 (*b*)	87–88 (ethanol)	45.65	3.92	20.01	$C_6H_6O_3S$	45.56	3.82	20.27
Ic	43 (*a*), 38 (*b*)	35–36 (subl.)	48.96	4.80	18.77	$C_7H_8O_3S$	48.82	4.68	18.62
Ie	41 (*a*), 46 (*b*)	105–108 (ether–hexane)	48.78	4.82	18.44	$C_7H_8O_3S$	48.82	4.68	18.62
If	36 (*b*)	Oily substance	53.62	6.15	16.31	$C_9H_{12}O_3S$	53.98	6.04	16.01
Ig	38 (*b*)	Oily substance	56.32	6.88	15.05	$C_{10}H_{14}O_3S$	56.05	6.59	14.96
VIIa	9.2	132–136 (ether)	49.12	5.22	18.01	$C_7H_8O_3S$	48.82	4.68	18.62
VIIIa	46	73–76 (ether)	49.04	4.99	18.45	$C_7H_8O_3S$	48.82	4.68	18.62

3-pentanoyl derivatives **Ie–g** with spectral characteristics that correlated with those of compounds **Ia, c** and were in agreement with the presumed structures. According to ^{1}H NMR spectra compounds **Ia, c, e–g** are fully enolized.



I, R^1 = H (**a, e, f**), Me (**c, g**); R^2 = Me (**a, c**), Et (**e**), Bu (**f, g**); **VI, R^1 = H (a–c, e, f)**, Me (**d, g**); R^2 = Me (**a–d**), Et (**e**), Bu (**f, g**); R^3 = All (**a, d–g**), Bu (**b**), 4-$MeOC_6H_4$ (**c**).

As with the other asymmetrical β-triketones in their ^{1}H NMR spectra appears a double set of signals from the proton-containing groups with the ratio of integral intensities from 1 : 3 to 1 : 8 corresponding to tautomeric forms A and B. It should be noted that for such compounds are taken into account two additional tautomers due to enolization of the carbonyl in the acyl side chain [7, 11]; however the spectral identification of the exo and endo enolized tautomeric forms of the cyclic β-triketones is still a debated topic.



The reaction of triketones **Ia, c, e–g** with allylamine, benzylamine, and *p*-anisidine as expected [7] proceeded at the carbonyl group of the acyl side chain affording enaminodiketones **VIa–g** (yield 75–90%) (Table 2). In the ^{1}H NMR spectra of the latter same as in the spectra of the initial triketones was observed a double set of signals due to the presence of two chelate enaminodicarbonyl forms **VIA, VIB**.

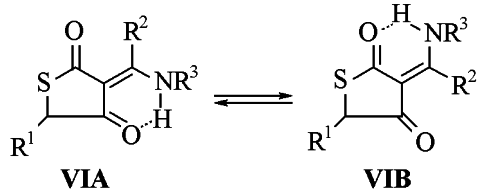


Table 2. Yields, melting points, and elemental analyses of exocyclic enaminodiketones **VIa**–**g**

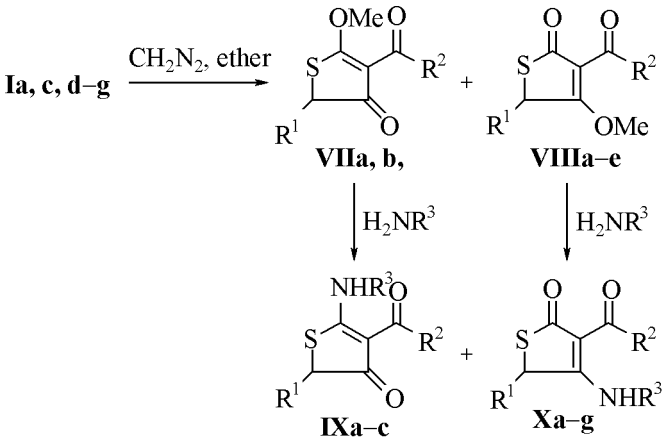
Compd. no.	Yield, %	mp, °C (solvent)	Found, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
VIa	86	66–67 (ether)	54.33	4.67	6.98	15.90	$C_9H_{11}NO_2S$	54.80	5.62	7.10	16.25
VIb	80	117–118 (ether)	63.72	5.50	5.21	13.08	$C_{13}H_{13}NO_2S$	63.14	5.30	5.66	12.96
VIc	75	136–138 (ether)	58.78	4.65	5.20	12.01	$C_{13}H_{13}NO_3S$	59.30	4.98	5.32	12.18
VId	78	152–154 (ether–hexane)	57.00	6.03	6.33	15.66	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18
VIe	90	Oily substance	56.88	6.45	7.01	15.04	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18
VIf	87	45–47 (heptane)	60.96	7.02	6.15	13.22	$C_{12}H_{17}NO_2S$	60.22	7.16	5.85	13.40
VIg	85	Oily substance	61.03	7.98	5.06	12.18	$C_{13}H_{19}NO_2S$	61.63	7.56	5.53	12.66

Table 3. Yields, melting points (from ethyl acetate–heptane), and elemental analyses of endocyclic enaminodiketones **IXa**–**c**, **Xa**–**g**, **XI**

Compd-no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
IXa	76	100–101	55.04	5.47	6.99	15.78	$C_9H_{11}NO_2S$	54.80	5.62	7.10	16.25
IXb	80	Oily substance	58.42	5.24	5.06	12.00	$C_{13}H_{13}NO_3S$	59.30	4.98	5.32	12.18
IXc	10	Oily substance	56.66	6.01	6.81	15.54	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18
Xa	87	96–98	55.17	5.56	6.97	15.55	$C_9H_{11}NO_2S$	54.80	5.62	7.10	16.25
Xb	84	120–121	63.22	5.15	5.09	12.76	$C_{13}H_{13}NO_2S$	63.14	5.30	5.66	12.96
Xc	90	126–128	59.44	5.27	5.31	12.12	$C_{13}H_{13}NO_3S$	59.30	4.98	5.32	12.18
Xd	60	Oily substance	57.09	6.52	6.15	15.76	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18
Xe	45	Oily substance	56.48	6.57	6.65	15.27	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18
Xf	42	35–37 [a]	60.12	7.06	5.91	13.03	$C_{12}H_{17}NO_2S$	60.22	7.16	5.85	13.40
Xg	33	Oily substance	61.71	7.08	5.47	12.86	$C_{13}H_{19}NO_2S$	61.63	7.56	5.53	12.66
XI	71[b], 85[c]	136–137	56.60	6.47	6.16	15.57	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18

[a] Solvent heptane. [b] From methyl ether **XIII**. [c] From methyl ether **VIIIa**.

It is known [7] that reacting with amines enol methyl ethers of β-triketones provides a possibility to change the direction of attack and to obtain through 1,4-vinylog substitution the enamino derivatives at the ring carbonyl group. We carried out various attempts for preparation of methyl ethers of 3-acylthiotetronic acids. Attempted alkylation of compounds **Ia, f** sodium salts with methyl iodide, dimethyl sulfate, or trimethyloxonium fluoborate from the reaction mixtures only the initial compounds were recovered.

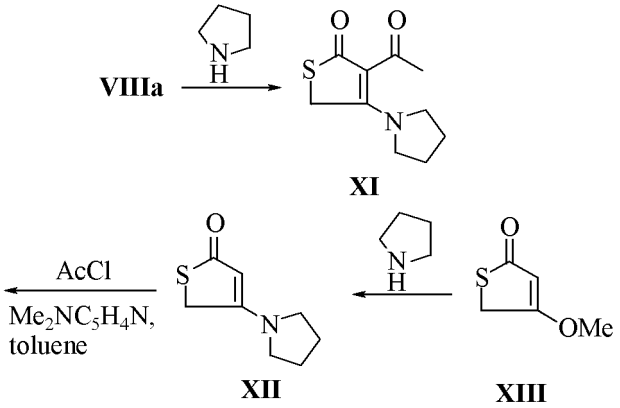


VII, VIII, R^1 = H (**a, c, d**), Me (**b, e**); R^2 = Me (**a, b**), Et (**c**), Bu (d, e); **IX**, R^1 = H (**a, b**), Me (**c**); R^2 = Me (**a**–**c**), R^3 = All (**a, c**), 4-$MeOC_6H_4$ (**b**); X, R^1 = H (**a**–**c, e**–**f**), Me (**d, g**); R^2 = Me (**a**–**d**), Et (**e**), Bu (**f, g**); R^3 = All (**a, d**–**g**), Bn (**b**), 4-$MeOC_6H_4$ (**c**).

The target products **VIIa, b, VIIIa–e** were detected by TLC only at treating triketones **Ia, c, e–g** with ether solution of diazomethane. However compounds **VIIb, VIIIb–e** were so unstable that we failed to isolate their samples for analysis. Therefore the ether solutions of compounds **VIIb, VIIIb–e** obtained by treating with diazomethane immediately were reacted with amines. We successfully isolated and characterized by spectral methods only regioisomeric methyl ethers of 3-acetylthiotetronic acid **VIIa** and **VIIIa** (Table 1). In the ^{1}H NMR spectra of ethers **VIIa** and **VIIIa** is lacking the enol proton signal at 16.00 ppm characteristic of the totally enolized initial β-triketone **Ia**, and appears a three-proton signal from methoxy group at 4.13 and 4.29 ppm respectively. In the IR spectra of compounds **VIIa** and **VIIIa** are observed absorption bands from conjugated carbonyl groups at 1650, 1675 and 1670, 1685 cm^{-1} respectively. The analysis of ^{1}H NMR spectra of regioisomeric methyl ethers of 3-halosubstituted thiotetronic acids [12] revealed that the methoxyvinyl group caused a stronger downfield shift of the signal from the neighboring C^5-methylene protons than a carbonyl group. Thus the methylene protons signal in the 2-methoxy derivatives is usually observed at 3.65–3.85 ppm whereas in the 4-methoxy derivatives these signals appear at 3.90–4.06 ppm. In our case the chemical shifts of the ring methylene protons are located at 3.78 ppm in compound **VIIa** and 4.07 ppm in compound **VIIIa** well consistent with the data from [12]. A similar correlation is also observed for the chemical shifts of C^5-methylene protons in the ^{1}H NMR spectra of the tautomeric A,B forms of 3-acyltetronic acids **Ia, e, f**. In the spectrum of the prevailing tautomer B the protons at C^5 appear at 4.03 ppm whereas those in the spectrum of A tautomer are located at 3.78–3.80 ppm. Unfortunately failed the attempt to confirm the structure of regioisomeric enol ethers **VIIa** and **VIIIa** by differential spectroscopy of nuclear Overhauser effect.

The reaction with allylamine and *p*-anisidine of the isolated in pure form methyl ethers of 3-acetyltetronic acid (**VIIa, VIIIa**) proceeded cleanly at room temperature and afforded in each case the corresponding endocyclic enaminodiketones **IXa, b, Xa, c**) in high yield (Table 3). Unlike that in reactions with allylamine of methyl ethers from triketones **Ic, e–g** that were brought into the reaction in situ we succeeded in separation and were able to characterize both regioisomeric enaminodiketones **IXc, Xd** originating only from triketone **Ic**. From the other triketones we obtained only enaminodiketones of **X** type. This is apparently due to the especially low stability of 2-methoxy derivatives from triketones **Ie–g**. The spectral characteristics of compounds obtained **IXa–c**, **Xa–h** are in full agreement with the assumed structure. In the ^{1}H NMR spectra are retained all the proton signals from the principal structural fragments of the molecule, disappear the methoxy group signals, and appear the proton signals from the introduced amino groups. Therewith in all spectra is observed a broadened proton signal from NH group in the 10–12 ppm region. In the IR spectra of enaminodiketones **IXa–c, Xa–g** the absorption bands of the N–H bond appear in the region 3100–3300 cm^{-1}, of enaminoketone moiety at 1470–1500 (C=C) and 1590–1630 cm^{-1} (C=O), and of a conjugated carbonyl group at 1655–1675 cm^{-1}.

Since the ^{1}H NMR data permitted us only indirect assignment of structure to regioisomeric enaminodiketones **IX, X** we attempted to prepare endocyclic enaminodiketone **XI** along two different routes: by



direct reaction of methyl ether **VIIIa** with pyrrolidine and by independent synthesis from enaminoketone **XII** through its acylation with acetyl chloride in the presence of 4-dimethylaminopyridine.

Enaminoketone **XII** was obtained by reaction of methyl ether **XIII** with pyrrolidine and by its physical constants corresponded to the substance described in [13]. Both at amination of methyl ether **VIIIa** with pyrrolidine and at acetylation of the pyrrolidine enaminoketone **XII** formed the same compound, enaminodiketone **XI** evidencing that the structures were correctly assigned proceeding from ^{1}H NMR spectra.

EXPERIMENTAL

IR spectra were recorded on UR-20 instrument from KBr pellets (with solid compounds) or thin films (with liquids). ^{1}H NMR spectra were registered on spectrometer Bruker AT-200 in $CDCl_3$, internal reference TMS. The melting points were measured on the Boëtius heating block. The reactions progress was monitored and the purity of compounds obtained was checked by TLC on Silufol UV-254 or Alufol UV-254 plates, development under UV irradiation followed by spraying with a solution of iron(III) chloride. For column chromatography was used silica gel 5–40 mesh (elutriated), 40–100 mesh (Chemapol), 40–60 mesh (Kieselgel 60, Merck), and neutral alumina (II grade Brockmann activity).

3-Acetyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (**Ia**), 3-ethoxycarbonyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (**Ib**), 3-acetyl-5-methyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (**Ic**), and 3-ethoxycarbonyl-5-methyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (**Id**) were prepared by the known procedure [3, 8]. The characteristics of the compounds obtained were consistent with those published in [3, 8–9].

(3*H*,5*H*)-Tetrahydrothiophene-2,4-dione (Va) and 5-methyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (Vb). A solution of 1 g (5.32 mmol) of 3-ethoxycarbonylthiotetronic acid (**Ib**) in 40 ml of 70% trifluoroacetic acid was boiled for 8–10 h (monitoring by TLC). After the end of the process the reaction mixture was evaporated. The oily residue was subjected to chromatography on silica gel (eluent ether). We obtained 0.57 g (92%) of crystalline compound **Va**, mp 124–127°C (mp 115–116°C [8]). In the same way from 1g (4.95 mmol) of compound **Id** was obtained 0.61 g (95%) 5-methyl-substituted compound **Vb** is yellow oily substance.

Acylation of thiotetronic acids Va and Vb. To a solution of 5 mmol of diketone **Va** or **Vb** in 30 ml of chloroform was added 0.8 ml (5.5 mmol) of triethylamine and 5.3 mmol of an appropriate acyl chloride. The mixture was stirred at room temperature till the disappearance of the initial diketone (TLC, eluent ether–hexane, 2 : 1). Then the mixture was acidified with 10 ml of 2 N hydrochloric acid, washed with water, saturated water solution of sodium hydrogen carbonate, dried with magnesium sulfate, and evaporated in a vacuum. The residue was the O-acylated derivative of compounds **Va, b**.

(a) The O-acyl derivative obtained was dissolved in 50 ml of toluene, 0.61 g (7.5 mmol) of 4-dimethylaminopyridine was added, and the mixture was left standing at room temperature for 3 days. Then the reaction mixture was treated with saturated water solution of sodium carbonate (5 × 15 ml), the water fractions were combined, washed with toluene, acidified to pH ~2 with 5% hydrochloric acid, the reaction product was extracted into toluene (4 × 20 ml). The combined organic solutions were dried with sodium sulfate and evaporated on a rotary evaporator. The residue was crystallized from methanol or from a mixture ethyl acetate–hexane.

(b) O-Acyl derivative was dissolved in 50 ml of acetonitrile, and thereto was added 1.4 ml (10.1 mmol) of triethylamine and 0.01 ml of acetone cyanohydrin. The reaction mixture was left overnight at room temperature, then the acetonitrile was distilled off under reduced pressure, the residue was dissolved in toluene and purified by conversion into a sodium salt as described under *a*. Yields, melting points, and elemental analyses of the obtained triketones **Ia, c, e–g** are given in Table 1.

3-Acetyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (Ia). IR spectrum, ν, cm^{-1}: 1700, 1675, 1630, 1585. ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3CO), 4.02 s (2H, CH_2S), 16.00 s (1H, OH).

3-Acetyl-5-methyl-(3*H*,5*H*)-tetrahydrothiophene-,4-dione (Ic). IR spectrum, ν, cm^{-1}: 1710, 1630, 1590. ^{1}H NMR spectrum, δ, ppm: 1.68 m (3H, CH_3S), 2.60 s (3H, CH_3CO), 4.02–4.18 m (1H, $\underline{CH}SCH_3$), 15.80 s (1H, OH).

3-Propanoyl-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (Ie). IR spectrum, ν, cm^{-1}: 1700, 1670, 1640, 1595, 1435, 1400. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, $\underline{CH}_3CH_2$, *J* 7.0 Hz), 3.00 q (3H, $CH_3\underline{CH}_2CO$, *J* 7.0 Hz), 4.02 s (2H, $\underline{CH}_2S$), 16.00 s (1H, OH).

3-Pentanoyl-2,4-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (If). IR spectrum, ν, cm^{-1}: 1700, 1640–1620, 1580, 1475, 1440, 1400. ^{1}H NMR spectrum, δ, ppm: 0.93 t (3H, $\underline{CH}_3CH_2$, *J* 7.0 Hz), 1.38 m

(2H, $CH_3\underline{CH}_2$), 1.64 m (2H, $CH_3CH_2\underline{CH}_2$), 2.94 t (2H, $\underline{CH}_2CO$, *J* 7.0 Hz), 3.97 s (2H, $\underline{CH}_2S$), 16.00 s (1H, OH).

5-Methyl-3-pentanoyl-(3*H*,5*H*)-tetrahydrothiophene2,4-dione (Ig). IR spectrum, ν, cm^{-1}: 1720–1700, 1630–1600, 1590–1580, 1470. ^1H NMR spectrum, δ, ppm: 0.95 t (3H, $\underline{CH}_3CH_2$, *J* 7.0 Hz), 1.20 m (2H, $CH_3\underline{CH}_2$), 1.62 m (2H, $CH_3CH_2\underline{CH}_2$), 1.70 d (3H, CH_3S, *J* 6.5 Hz), 2.98 t (2H, CH_2CO, *J* 7.0 Hz), 4.18 q (1H, $\underline{CH}SCH_3$, *J* 6.5 Hz), 14.00 s (1H, OH).

Exocyclic enaminodiketones VIa–g. To a solution of 3 mmol of compound **Ia, c, e–g** in 50 ml of benzene was added 1.5-fold excess of an appropriate amine, and the mixture was boiled for 30 min and left overnight at room temperature. The solvent and excess amine were removed in a vacuum, and the residue was purified by column chromatography on alumina (eluent ethyl acetate–hexane–chloroform). Yields, melting points, and elemental analyses of enaminodiketones obtained are presented in Table 2.

3-[1-(Allylamino)ethylidene]-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (VIa). IR spectrum, ν, cm^{-1}: 2930, 1650, 1610, 1590. ^1H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 3.68 s and 3.74 s (2H, CH_2S), 4.08 t (2H, NCH_2, *J* 6.0 Hz), 5.12 m (2H, CH_2=), 5.90 · (1H, CH=), 11.44 br.s and 12.24 br.s (1H, NH).

3-[1-(Benzylamino)ethylidene]-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (VIb). IR spectrum, ν, cm^{-1}: 3200, 1670, 1650, 1600, 1570. ^1H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 3.68 s and 3.74 s (2H, CH_2S), 4.66 t (2H, NCH_2, *J* 6.0 Hz), 7.28 m (2H arom), 7.39 m (3H arom), 11.5 br.s (1H, NH).

3-[1-(4-Methoxyphenylamino)ethylidene]-(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (VIc). IR spectrum, ν, cm^{-1}: 3100–2850, 1670, 1610, 1590. ^1H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 3.75 s and 3.84 s (2H, CH_2S), 3.88 s (3H, OMe), 6.90 d (2H arom, *J* 7.2 Hz), 7.12 d (3H arom, *J* 7.0 Hz), 12.70 br.s and 13.50 br.s (1H, NH).

3-[1-(Allylamino)ethylidene]-5-methyl(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (VId). IR spectrum, ν, cm^{-1}: 3200, 1665, 1605. ^1H NMR spectrum, δ, ppm: 1.60 m (3H, $\underline{CH}_3CHS$), 2.60 s (3H, $\underline{CH}_3CNH$), 3.90 m (1H, CHS), 4.10 m (2H, $\underline{CH}_2NH$), 5.30 m (2H, CH_2=), 5.90 m (1H, CH=), 11.50 br.s and 12.25 br.s (1H, NH).

3-[1-(Allylamino)propylidene]-(3*H*,5*H*)tetrahydrothiophene-2,4-dione (VIe). IR spectrum, ν, cm^{-1}: 2960, 2940, 2860, 1675, 1605, 1500. ^1H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3, *J* 7.2 Hz), 3.03 q (2H, $\underline{CH}_2CH_3$, *J* 7.2 Hz), 3.65 s and 3.74 s (2H, CH_2S), 4.15 t (2H, NCH_2, *J* 6.0 Hz), 5.28–5.34 s (2H, CH_2=), 5.90 s (1H, CH=), 11.40 br.s and 12.23 br.s (1H, NH).

3-[1-(Allylamino)pentylidene]-(3*H*,5*H*)tetrahydrothiophene-2,4-dione (VIf). IR spectrum, ν, cm^{-1}: 2970, 2940, 2880, 1675, 1610, 1500. ^1H NMR spectrum, δ, ppm: 0.97 t (3H, $\underline{CH}_3CH_2$, *J* 7.2 Hz), 1.50 s (4H, $\underline{CH}_2\underline{CH}_2CH_3$), 3.67 s and 3.74 s (2H, CH_2S), 4.15 t (2H, NCH_2, *J* 6.0 Hz), 5.27 d (*J* 6.5 Hz) and 5.37 s (2H, CH_2=), 5.92 m (1H, CH=), 11.40 br.s and 12.22 br.s (1H, NH).

3-[1-(Allylamino)pentylidene]-5-methyl(3*H*,5*H*)-tetrahydrothiophene-2,4-dione (VIg). IR spectrum, ν, cm^{-1}: 3250–3200, 1670, 1600, 1500. ^1H NMR spectrum, δ, ppm: 0.96 t (3H, $\underline{CH}_3CH_2$, *J* 7.2 Hz), 1.52 m (4H, $CH_2\underline{CH}_2CH_3$), 1.58 d (*J* 6.5 Hz) and 1.60 d (*J* 6.5 Hz) (3H, $SCH\underline{CH}_3$), 3.85 q (*J* 6.5 Hz) and 3.95 q (*J* 6.5 Hz) (1H, CHS), 4.09 t (2H, NCH_2, *J* 6.0 Hz), 5.30– 5.35 m (2H, CH_2=), 5.88 m (1H, CH=), 11.44 br.s and 12.22 br.s (1H, NH).

Enol methyl ethers VIIa, VIIIa. In 100 ml of ethyl ether was dissolved 5 g (31.6 mmol) of 3-acetylthiotetronic acid (**Ia**), the solution was cooled to 0°C, and at continuous stirring was added an ether solution of diazomethane till TLC showed complete disappearance of the initial triketone. The ether was distilled off, the residue was diluted with benzene. The precipitated yellow solid that rapidly turned dark in air was separated, and washed with ether on the filter. We obtained 0.5 g of 2-methoxy derivative **VIIa**. The organic solution was evaporated, and the residue was crystallized from ether to afford 2.5 g of yellow crystals of 4-methoxy derivative **VIIIa**. Yields, melting points, and elemental analyses of ethers obtained are given in Table 1.

3-Acetyl-2-methoxy-(3*H*)-dihydrothiophene-4-one (VIIa). IR spectrum, ν, cm^{-1}: 1650, 1610, 1490, 1445. ^1H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 3.78 s (2H, CH_2), 4.29 s (3H, CH_3O).

3-Acetyl-4-methoxy-(5*H*)-dihydrothiophene-2-one (VIIIa). IR spectrum, ν, cm^{-1}: 1685, 1635, 1570, 1450, 1400. ^1H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 4.07 s (2H, CH_2), 4.13 s (3H, CH_3O).

Endocyclic enaminodiketones IXa–c, Xa–g. To a solution of 0.1 g (0.58 mmol) of methyl ether **VIIa**

or **VIIIa** in 30 ml of benzene was added 1.5-fold excess (0.87 mmol) of an appropriate amine, and the mixture was left overnight at room temperature. The benzene solution was washed with 10 ml of 5% hydrochloric acid and water, dried with sodium sulfate. The benzene was distilled off in a vacuum, the residue was crystallized from ethyl acetate–heptane mixture. Thus were obtained enaminodiketones **IXa, b, Xa–c**.

Enaminodiketones from compounds **Ic, e–g** were prepared from the ether solution of the enol methyl ethers mixture obtained by treating along above described procedure of 1.5 mmol of the appropriate triketone with the ether solution of diazomethane. This ether solution was treated with the 1.5-fold excess (1.7 mmol, 2.25 ml) of allylamine, and from the reaction mixture were isolated by column chromatography on alumina (eluent toluene) enaminodiketones **IXc, Xd–g**. Yields, melting points, and elemental analyses of products **IXa–c, Xa–g** are listed in Table 3.

2-Allylamino-3-acetyl-(3*H*)-dihydrothiophene-2-one (IXa). IR spectrum, ν, cm^{-1}: 3160, 1650, 1595, 1570. ^1H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 3.67 s (2H, CH_2S), 4.04 t (2H, NCH_2, *J* 6.0 Hz), 5.36 m (2H, CH_2=), 5.90 m (1H, CH=), 11.18 br.s (1H, NH).

3-Acetyl-2-(4-methoxyphenylamino)-(3*H*)-dihydrothiophene-2-one (IXb). IR spectrum, ν, cm^{-1}: 3150, 1635, 1620, 1600, 1580, 1520. ^1H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 3.64 s (2H, CH_2S), 3.86 s (3H, OCH_3), 7.20 d (2H arom, *J* 9.0 Hz), 7.28 d (2H arom, *J* 9.0 Hz), 12.60 br.s (1H, NH).

2-Allylamino-3-acetyl-5-methyl-(3*H*)-dihydrothiophene-2-one (IXc). IR spectrum, ν, cm^{-1}: 3200, 1685, 1655, 1620, 1590. ^1H NMR spectrum, δ, ppm: 1.62 d (3H, $\underline{CH}_3CHS$, *J* 6.5 Hz), 2.51 s (3H, CH_3), 3.80 q (1H, $CH_3\underline{CH}S$, *J* 6.5 Hz), 4.06 t (2H, $\underline{CH}_2NH$, *J* 6.0 Hz), 5.25–5.40 m (2H, CH_2=), 5.96 m (1H, CH=), 11.16 br.s (1H, NH).

4-Allylamino-3-acetyl-(5*H*)-dihydrothiophene-2-one (Xa). IR spectrum, ν, cm^{-1}: 3195, 1640, 1615, 1580. ^1H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 3.98 s (2H, CH_2S), 4.06 t (2H, NCH_2, *J* 6.0 Hz), 5.32 m (2H, CH_2=), 5.90 m (1H, CH=), 11.00 br.s (1H, NH).

3-Acetyl-4-benzylamino-(5*H*)-dihydrothiophene-2-one (Xb). IR spectrum, ν, cm^{-1}: 3200, 1660, 1610, 1500. ^1H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 3.98 s (2H, CH_2S), 4.60 d (2H, NCH_2, *J* 6.0 Hz), 7.20–7.45 m (5H, C_6H_5), 11.28 br.s (1H, NH).

3-Acetyl-4-(4-methoxyphenylamino)-(5*H*)-dihydrothiophene-2-one (Xc). IR spectrum, ν, cm^{-1}: 3100, 1660, 1625, 1570, 1520. ^1H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 3.87 s (3H, OCH_3), 3.90 s (2H, CH_2S), 6.97 d (2H arom, *J* 9.0 Hz), 7.17 d (2H arom, *J* 9.0 Hz), 12.24 br.s (1H, NH).

4-Allylamino-3-acetyl-5-methyl-(5*H*)dihydrothiophene-2-one (Xd). IR spectrum, ν, cm^{-1}: 3100, 1640, 1610, 1590, 1520. ^1H NMR spectrum, δ, ppm: 1.72 d (3H, $\underline{CH}_3CHS$, *J* 6.5 Hz), 2.52 s (3H, CH_3), 4.16 t (2H, $\underline{CH}_2NH$, *J* 6.0 Hz), 4.40 q (1H, $CH_3\underline{CH}S$, *J* 6.5 Hz), 5.25–5.40 m (2H, CH_2=), 5.96 m (1H, CH=), 11.26 br.s (1H, NH).

4-Allylamino-3-propanoyl-(5*H*)-dihydrothiophene-2-one (Xe). IR spectrum, ν, cm^{-1}: 3200, 3100, 1685, 1655, 1620, 1590. ^1H NMR spectrum, δ, ppm: 1.12 t (3H, CH_3, *J* 7.2 Hz), 2.98 q (2H, $\underline{CH}_2CH_3$, *J* 7.2 Hz), 3.98 s (2H, CH_2S), 4.04 t (2H, NCH_2, *J* 6 Hz), 5.25–5.40 m (2H, CH_2=), 5.95 m (1H, CH=), 11.10 br.s (1H, NH).

4-Allylamino-3-pentanoyl-(5*H*)-dihydrothiophene-2-one (Xf). IR spectrum, ν, cm^{-1}: 3100, 1675, 1630, 1590. ^1H NMR spectrum, δ, ppm: 0.91 t (3H, $\underline{CH}_3CH_2$, *J* 7 Hz), 1.36 m (2H, $\underline{CH}_2CH_3$), 1.58 m (2H, $\underline{CH}_2CH_2CH_3$), 2.94 t (2H, CH_2CO, *J* 7 Hz), 3.96 s (2H, CH_2S), 4.04 t (2H, NCH_2, *J* 6 Hz), 4.32 q (1H, CHS), 5.30 m and 5.36 m (2H, CH_2=), 5.91 m (2H, CH=), 11.15 s (1H, NH).

4-Allylamino-5-methyl-3-pentanoyl-(5*H*)dihydrothiophene-2-one (Xg). IR spectrum, ν, cm^{-1}: 3100, 1675, 1625, 1590. ^1H NMR spectrum, δ, ppm: 0.90 t (3H, $\underline{CH}_3CH_2$, *J* 7.2 Hz), 1.35 m (2H, $\underline{CH}_2CH_3$), 1.56 m (2H, $\underline{CH}_2CH_2CH_3$), 1.67 d (3H, $SCH\underline{CH}_3$, *J* 7.0 Hz), 2.94 t (2H, CH_2CO, *J* 7.2 Hz), 4.09 t (2H, NCH_2, *J* 6.0 Hz), 4.32 q (1H, CHS, *J* 7.0 Hz), 5.30–5.36 m (2H, CH_2=), 5.91 m (2H, CH=), 11.35 br.s (1H, NH).

3-Acetyl-4-pyrrolidino-(5H)-dihydrothiophene-2-one (XI). To a solution of 0.12 g (1 mmol) of diketone **Va** in 15 ml of 5% hydrogen chloride solution in methanol was added 0.12 ml (1.1 mmol) of trimethyl orthoformate, and the mixture was kept at room temperature under anhydrous conditions for 48 h (TLC monitoring). On completion of the reaction the solvent was removed in a vacuum, and the residue was diluted with water (20 ml).The methyl ether was extracted with ethyl ether (2 × 30 ml), the extract was washed with 2% solution of sodium

hydrogen carbonate, and dried with sodium sulfate. On removing the solvent the residual crude methyl ether **XIII** (0.11 g, yield 85%) was dissolved in 10 ml of pyrrolidine and left standing at room temperature for 36 h. Then the reaction mixture was diluted with hexane and kept at 0°C for 8 h. Crystalline enamine **XII** was separated from the solution and washed with cold ether on the filter. We obtained 0.11 g (80%) of compound **XII** identical by physical characteristics to the compound described in [13].

To a solution of 0.11 g (0.68 mmol) of enamine-ketone **XII** in 50 ml of anhydrous toluene was added 1.6 ml (2 mmol) of acetyl chloride and 2.49 g (2.04 mmol) of dimethylaminopyridine. The mixture was boiled for 16 h under anhydrous conditions and left overnight at room temperature. Then the reaction mixture was shaken with 30 ml of water, the organic layer was separated, washed with 10% hydrochloric acid, 2% solution of sodium carbonate, and dried with magnesium sulfate. The solvent was evaporated in a vacuum, the residue was purified by column chromatography on alumina (eluent ethyl acetate–hexane). We obtained 0.1 g of 3-acetyl-4-pyrrolidino-(5*H*)-dihydrothiophene-2-one (**XI**) as light-yellow crystals recrystallized from a mixture ethyl acetate–heptane. IR spectrum, ν, cm^{-1}: 1640, 1600, 1580, 1520, 1480. ^1H NMR spectrum, δ, ppm: 2.03 m (4H, $\underline{CH}_2CH_2NCH_2\underline{CH}_2$), 2.51 s (3H, CH_3), 3.19 t (2H, NCH_2, *J* 6 Hz), 3.60 t (2H, NCH_2, *J* 6 Hz), 3.92 s (2H, CH_2S).

An identical compound was obtained by treating 0.1 g (0.58 mmol) of methyl ether **VIIIa** with 0.1 ml (1.2 mmol) of pyrrolidine by the procedure for the synthesis of the endocyclic enaminodiketones. Yields, melting point, and elemental analyses of compound **XI** are given in Table 3.

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