Russian Journal of Organic Chemistry, Vol. 39, No. 12, 2003, pp. 1772–1776. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 12, 2003, pp. 1844–1847.

4-Acyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones: Synthesis, Oxidation, and Reaction with Amines

T. A. Zheldakova, M. V. Budnikova, I. L. Rubinova, and D. B. Rubinov

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, ul. Kuprevicha 5/2, Minsk, 220141 Belarus
e-mail: rubinov@iboch.bas-net.by

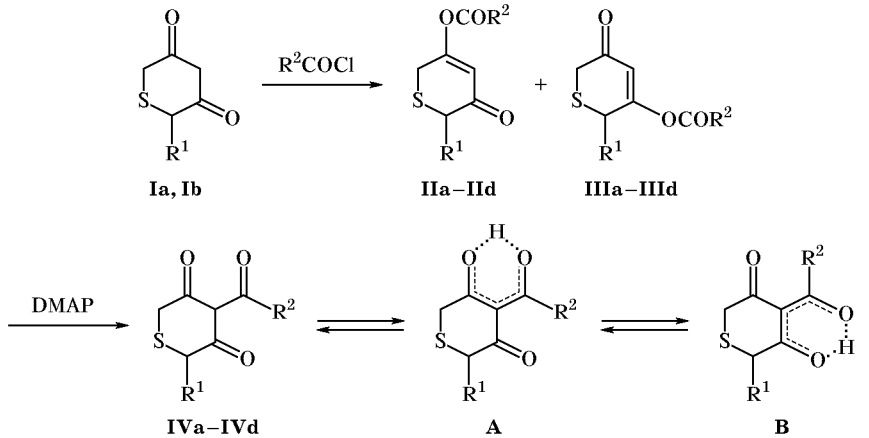
Received March 13, 2003

Abstract—Acylation of 2*H*-thiopyran-3,5(4*H*,6*H*)-dione and 2-methyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione with acetyl chloride or propionyl chloride afforded the corresponding 4-acyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones. Oxidation of 4-acetyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione with *m*-chloroperoxybenzoic acid gave 4-acetyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione 1-oxide. 4-Acyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones and 4-acetyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione 1-oxide reacted with pyrrolidine, allylamine, and *p*-anisidine, resulting in formation of the corresponding 4-aminomethylene derivatives.

Heterocyclic β-diketones of the thiopyran series, specifically 2*H*-thiopyran-3,5(4*H*,6*H*)-diones **I**, have been studied to a considerably lesser extent than six-membered alicyclic β-diketones (1,3-cyclohexanediones). However, some thiopyran-3,5-dione derivatives were found to exhibit herbicide [1–2], antitumor, and antiapoptose activity [3] and to regulate permeability of cell membranes [4]. A procedure for the synthesis of thio analogs of steroids possessing antiphlogistic properties was proposed on the basis of thiopyran-3,5-diones [5].

We previously showed that β-tricarbonyl compounds of the 3-acyl-2,4(3*H*,5*H*)-thiophenedione (thiotetronic acid) [6] and 3-acyldihydro-2*H*-thiopyran-2,4(3*H*)-dione series [7] can be used in the synthesis of N,S-dihetero analogs of steroids. While extending studies in this line, we have developed a simple procedure for the preparation of 4-acyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones and examined some their chemical properties. The initial compounds, 2*H*-thiopyran-3,5-(4*H*,6*H*)-dione (**Ia**) and 2-methyl-2*H*-thiopyran-3,5-(4*H*,6*H*)-dione (**Ib**), were synthesized by the procedure described in [8]. Acylation of diketones **Ia** and **Ib** with acetyl chloride and propionyl chloride in the presence of pyridine gave mixtures of regioisomeric enol esters **IIa**–**IId** and **IIIa**–**IIId** which

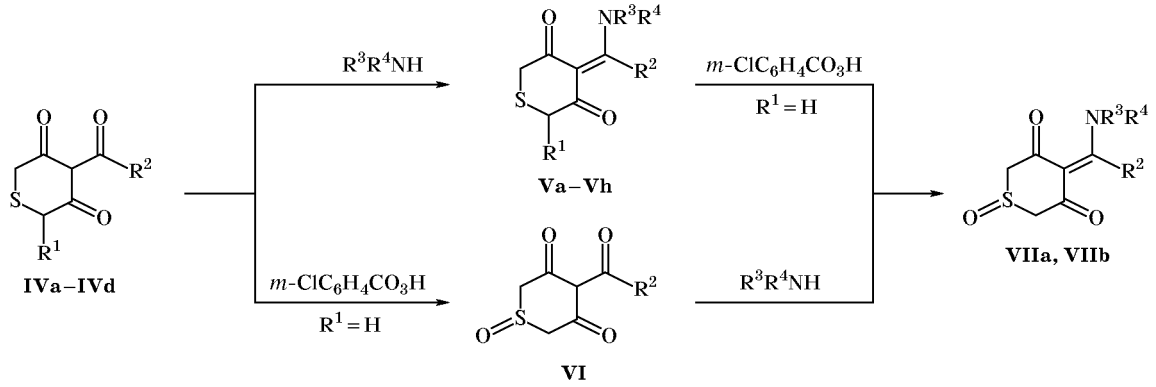
Scheme 1.



I, R^1 = H (**a**), Me (**b**); **II**–**IV**, R^1 = H, R^2 = Me (**a**); R^1 = H, R^2 = Et (**b**); R^1 = R^2 = Me (**c**); R^1 = Me, R^2 = Et (**d**).

1070-4280/03/3912-1772 $25.00 © 2003 MAIK "Nauka / Interperiodica"

Scheme 2.



V, R^1 = H, R^2 = Me, R^3R^4 = $(CH_2)_4$ (**a**); R^1 = H, R^2 = Et, R^3R^4 = $(CH_2)_4$ (**b**); R^1 = R^2 = Me, R^3R^4 = $(CH_2)_4$ (**c**); R^1 = R^3 = H, R^2 = Me, R^4 = $CH_2CH{=}CH_2$ (**d**); R^1 = R^3 = H, R^2 = Et, R^4 = $CH_2CH{=}CH_2$ (**e**); R^1 = R^2 = Me, R^3 = H, R^4 = $CH_2CH{=}CH_2$ (**f**); R^1 = R^3 = H, R^2 = Me, R^4 = *p*-$MeOC_6H_4$ (**g**); R^1 = R^2 = Me, R^3 = H, R^4 = *p*-$MeOC_6H_4$ (**h**); **VII**, R^2 = Me, R^3 = H, R^4 = $CH_2CH{=}CH_2$ (**a**); R^2 = Me, R^3 = H, R^4 = *p*-$MeOC_6H_4$ (**b**).

were subjected (without isolation) to O–C-isomerization to the target 4-acylthiopyran-3,5-diones **IVa**–**IVd** by the action of 4-dimethylaminopyridine (DMAP) (Scheme 1).

Triketones **IVa**–**IVd** are completely enolized, as follows from the presence in their ^{1}H NMR spectra of a characteristic downfield signal at δ 18 ppm, which belongs to proton of the enol hydroxy group (H-chelate moiety; structure **A**). Unsymmetrical β-triketones **IVc** and **IVd** give rise to a double set of signals in the ^{1}H NMR spectra due to equilibrium between two enol forms **A** and **B**. The IR spectra of triketones **IVa** and **IVb** contain a strong absorption band at 1670–1680 cm^{-1}, corresponding to the conjugated carbonyl group, and a very strong band in the region 1550–1570 cm^{-1}, which belong to stretching vibrations of the chelating carbonyl group and conjugated double bond. Unsymmetrical triketones **IVc** and **IVd** additionally showed in the IR spectra a weak carbonyl absorption at 1720 cm^{-1} due to non-enolized C=O group.

We planned to use the resulting β-triketones of the thiopyran series in the synthesis of Schiff bases [6, 7]. Therefore, we examined their reactions with amines. Like β-triketones of the cyclohexane series [9], 4-acyl-2*H*-thiopyran-3,5-(4*H*,6*H*)-diones **IVa**–**IVd** readily reacted with pyrrolidine, allylamine, and *p*-anisidine to give compounds **Va**–**Vh** having an exocyclic enamino group (Scheme 2). The ^{1}H NMR spectra of compounds **Va**–**Vh** contained signals from protons in the substituents at the nitrogen atom, but no enol proton signal at δ 18–19 ppm was present. Instead, a broadened signal from the NH proton appeared at δ 12–13 ppm. The structure of enamino diketones **Va**–**Vh** was also confirmed by the IR and mass spectra and elemental analyses.

The presence of a sulfur atom in molecules of compounds **IV** and **V** makes it possible to extend the range of their synthetic transformations. It is known [10] that β-diketones of the thiopyran series can be oxidized to the corresponding sulfoxides by the action of peroxybenzoic acid. β-Triketones derived from cyclohexane react with *m*-chloroperoxybenzoic acid to give a complex mixture of products which are difficult to identify [11]. Therefore, the results of oxidation of β-triketones **IV** and **V** could not be predicted. By reaction of 4-acetyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**IVa**) with *m*-chloroperoxybenzoic acid in chloroform in 0°C we obtained sulfoxide **VI** whose IR, ^{1}H NMR, and mass spectra were consistent with the assumed structure. Like triketones **IV**, sulfoxide **VI** reacted with allylamine and *p*-anisidine to afford the corresponding enamino derivatives at the acetyl carbonyl group (compounds **VIIa** and **VIIb**). The product obtained by oxidation of enamine **Va** with *m*-chloroperoxybenzoic acid was identical in physical properties to sulfoxide **VIIa**.

We also made an attempt to effect the reaction with amines at the ring carbonyl group. This is usually achieved via transformation of β-triketones into methyl enol ethers [9]. However, treatment of both 4-acyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones **IVa**–**IVd** and sulfoxide **VI** with methylating agents, such as diazomethane in diethyl ether or dimethyl sulfate in the presence of potassium carbonate, resulted in formation of a complex mixture of compounds, from which we failed to isolate the desired products.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as KBr pellets (solid substances) or thin films (liquids). The ^{1}H NMR spectra were recorded on a Bruker AT-200 instrument from solutions in chloroform-*d* containing TMS as internal reference. The mass spectra were measured on an MKh-1320 mass spectrometer. The melting points were determined on a Boetius device. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 or Alufol UV-254 plates; spots were visualized under UV light with subsequent spraying with a solution of iron(III) chloride. Silica gel 5/40 μm (elutriated) was used for column chromatography.

Acylation of diketones Ia and Ib. To a solution of 30 mmol of diketone **Ia** or **Ib** in 100 ml of toluene we added with stirring 2.9 ml (36 mmol) of anhydrous pyridine and 33 mmol of acetyl or propionyl chloride. The mixture was stirred for 3 h at room temperature (until the initial compound disappeared according to the TLC data), and 50 ml of cold water was added. The organic layer was separated, washed with a 1% solution of Na_2CO_3, dried over magnesium sulfate, and evaporated on a rotary evaporator. The residue (*O*-acyl derivative, 30 mmol) was dissolved in 100 ml of dry toluene, 0.7 g (6 mmol) of 4-dimethylaminopyridine was added, and the mixture was stirred for 16–20 h (TLC) with protection from atmospheric moisture. The mixture was then washed with 10% hydrochloric acid (2 × 20 ml), the organic phase was separated, and the aqueous phase was extracted with toluene (2 × 20 ml). The combined extracts were washed with a 10% solution of Na_2CO_3 and dried over magnesium sulfate, and the solvent was removed on a rotary evaporator.

4-Acetyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (IVa). Yield 4.90 g (95%). Low-melting colorless crystals, mp 24–25°C (from hexane). IR spectrum, ν, cm^{-1}: 1675, 1560. ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 3.38 s (2H, CH_2), 3.52 s (2H, CH_2), 18.2 s (1H, enol). Found, %: C 48.98; H 4.80; S 18.46. $[M]^+$ 172. $C_7H_8O_3S$. Calculated, %: C 48.82; H 4.68; S 18.62.

4-Propionyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (IVb). Yield 3.60 g (65%). Oily substance. IR spectrum, ν, cm^{-1}: 1670, 1560. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3, J = 7.0 Hz), 3.04 q (2H, CH_2, J = 7.0 Hz), 3.40 s (2H, CH_2), 3.52 s (2H, CH_2), 18.50 s (1H, enol). Found, %: C 51.81; H 5.63; S 17.02. $[M]^+$ 186. $C_8H_{10}O_3S$. Calculated, %: C 51.60; H 5.41; S 17.22.

4-Acetyl-2-methyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (IVc). Yield 5.00 g (90%). Oily substance. IR spectrum, ν, cm^{-1}: 1720, 1680, 1560. ^{1}H NMR spectrum, δ, ppm: 1.50 d and 1.60 d (3H, CH_3, J = 7.0 Hz); 2.60 s (3H, CH_3); 3.48 q and 3.60 q (1H, CH, J = 7.0 Hz); 3.45 s, 3.48 d, and 3.75 d (2H, SCH_2, J = 18 Hz); 18.2 s and 18.4 s (1H, enol). Found, %: C 51.67; H 5.56; S 17.34. $[M]^+$ 186. $C_8H_{10}O_3S$. Calculated, %: C 51.60; H 5.41; S 17.22.

2-Methyl-4-propionyl-2*H*-thiopyran-3,5-(4*H*,6*H*)-dione (IVd). Yield 3.70 g (62%). Oily substance. IR spectrum, ν, cm^{-1}: 1720, 1680, 1560. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3, J = 7.0 Hz); 1.45 d and 1.58 d (3H, CH_3, J = 7.0 Hz); 3.02 m (2H, CH_3); 3.46 s, 3.48 d, and 3.74 d (2H, CH_2S, J = 18.0 Hz), 3.47 q and 3.62 q (1H, CH, J = 7.0 Hz); 18.4 s and 18.6 s (1H, enol). Found, %: C 54.07; H 6.16; S 16.20. $[M]^+$ 200. $C_9H_{12}O_3S$. Calculated, %: C 53.98; H 6.04; S 16.01.

Enamines Va–Vh. To a solution of 1 mmol of β-triketone **IVa–IVd** in 25 ml of toluene we added 1.3 mmol of the corresponding amine, and the mixture was heated for 2–3 h under reflux (TLC). The mixture was then poured into water and washed with dilute hydrochloric acid. The organic phase was separated, and the aqueous phase was extracted with chloroform (2 × 10 ml). The extracts were combined with the organic phase and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate–hexane.

4-(1-Pyrrolidinoethylidene)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Va). Yield 0.20 g (89%), mp 98–99°C. IR spectrum, ν, cm^{-1}: 1630, 1580, 1550. ^{1}H NMR spectrum, δ, ppm: 2.80 m (4H, C**H**$_2$C**H**$_2$CH$_2$), 2.50 s (3H, CH_3), 3.30 s (4H, CH_2SCH_2), 3.72 m (4H, CH_2NCH_2). Found, %: C 58.95; H 6.91; N 6.32; S 14.06. $[M]^+$ 225. $C_{11}H_{15}NO_2S$. Calculated, %: C 58.64; H 6.71; N 6.22; S 14.23.

4-(1-Pyrrolidinopropylidene)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Vb). Yield 0.19 g (78%), mp 65–67°C. IR spectrum, ν, cm^{-1}: 1670, 1630, 1580, 1540. ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, CH_3, J = 7.0 Hz), 2.10 m (4H, C**H**$_2$C**H**$_2$CH$_2$), 2.96 q (2H, C**H**$_2$CH$_3$, J = 7.0 Hz), 3.30 s (4H, CH_2SCH_2), 3.82 m (4H, CH_2NCH_2). Found, %: C 60.47; H 7.31; N 6.02; S 13.26. $[M]^+$ 239. $C_{12}H_{17}NO_2S$. Calculated, %: C 60.22; H 7.16; N 5.85; S 13.40.

2-Methyl-4-(1-pyrrolidinoethylidene)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Vc). Yield 0.21 g (88%). Oily substance. IR spectrum, ν, cm^{-1}: 1630, 1580, 1540. ^{1}H NMR spectrum, δ, ppm: 1.50 d (3H,

C**H**$_3$CH, *J* 7.0 Hz), 2.06 m (4H, C**H**$_2$C**H**$_2$CH$_2$), 2.46 s (3H, CH$_3$), 3.36 q (1H, CH, *J* = 7.0 Hz), 3.28–3.44 m (2H, CH$_2$S, *J* = 18.0 Hz), 3.68 m (4H, CH$_2$NCH$_2$). Found, %: C 60.47; H 7.34; N 5.98; S 13.56. $[M]^+$ 239. $C_{12}H_{17}NO_2S$. Calculated, %: C 60.22; H 7.16; N 5.85; S 13.40.

4-(1-Allylaminoethylidene)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Vd). Yield 0.20 g (95%), mp 61–62°C. IR spectrum, ν, cm^{-1}: 3180, 1650, 1585. ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH$_3$), 3.36 s (4H, CH$_2$SCH$_2$), 4.16 m (2H, CH$_2$N), 5.25 m (2H, CH$_2$=), 5.86 m (1H, CH=), 13.2 br.s (1H, NH). Found, %: C 57.01; H 6.45; N 6.48; S 15.36. $[M]^+$ 211. $C_{10}H_{13}NO_2S$. Calculated, %: C 56.85; H 6.20; N 6.63; S 15.18.

4-(1-(Allylaminopropylidene)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Ve). Yield 0.21 g (93%), mp 50–52°C. IR spectrum, ν, cm^{-1}: 3200, 1650, 1580. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH$_3$, *J* = 7.0 Hz), 2.92 q (2H, C**H**$_2$CH$_3$, *J* = 7.0 Hz), 3.36 s (4H, CH$_2$SCH$_2$), 4.12 m (2H, CH$_2$N), 5.26 m (2H, CH$_2$=), 5.90 m (1H, CH=), 13.16 br.s (1H, NH). Found, %: C 58.82; H 6.95; N 6.18; S 14.06. $[M]^+$ 225. $C_{11}H_{15}NO_2S$. Calculated, %: C 58.64; H 6.71; N 6.22; S 14.23.

4-(1-Allylaminoethylidene)-2-methyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Vf). Yield 0.18 g (80%). Oily substance. IR spectrum, ν, cm^{-1}: 3300, 1650, 1580. ^{1}H NMR spectrum, δ, ppm: 1.48 d (3H, C**H**$_3$CH, *J* = 7.0 Hz), 2.48 s (3H, CH$_3$), 3.42 q (1H, C**H**CH$_3$, *J* 7.0 Hz), 3.34 d and 3.50 d (2H, SCH$_2$, *J* = 18.0 Hz), 4.08 m (2H, CH$_2$N), 5.28 m (2H, CH$_2$=), 5.88 m (1H, CH=), 13.12 br.s (1H, NH). Found, %: C 58.52; H 6.87; N 6.38; S 14.46. $[M]^+$ 225. $C_{11}H_{15}NO_2S$. Calculated, %: C 58.64; H 6.71; N 6.22; S 14.23.

4-[1-(4-Methoxyphenylamino)ethylidene]-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Vg). Yield 0.26 g (93%), mp 120–121°C. IR spectrum, ν, cm^{-1}: 3160, 1645, 1620, 1580. ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH$_3$), 3.40 s (4H, 2CH$_2$), 3.86 s (3H, OCH$_3$), 7.02 m (4H, H$_{arom}$), 14.4 br.s (1H, NH). Found, %: C 60.72; H 5.68; N 5.12; S 11.46. $[M]^+$ 227. $C_{14}H_{15}NO_3S$. Calculated, %: C 60.63; H 5.45; N 5.05; S 11.56.

4-[1-(4-Methoxyphenylamino)ethylidene]-2-methyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (Vh). Yield 0.25 g (85%). Oily substance. IR spectrum, ν, cm^{-1}: 3160, 1645, 1620, 1580. ^{1}H NMR spectrum, δ, ppm: 1.56 d (3H, CH$_3$, *J* = 7.0 Hz), 2.44 s (3H, CH$_3$), 3.50 q (1H, CH, *J* = 7.0 Hz), 3.42 d and 3.60 d (2H, SCH$_2$, 3H, CH$_3$, *J* = 18.0 Hz), 3.84 s (3H, OCH$_3$), 7.00 m (4H, H$_{arom}$), 14.46 br.s (1H, NH). Found, %: C 62.02; H 5.98; N 4.62; S 11.16. $[M]^+$ 291. $C_{15}H_{17}NO_3S$. Calculated, %: C 61.83; H 5.88; N 4.81; S 11.01.

4-Acetyl-2*H*-1λ^4-thiopyran-3,5(4*H*,6*H*)-dione 1-oxide (VI). To a solution of 0.17 g (1 mmol) of triketone **IVa** in 10 ml of chloroform we added at 0°C 1.1 mmol of *m*-chloroperoxybenzoic acid, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using chloroform as eluent. Yield 0.14 g (75%), mp 83–84°C. IR spectrum, ν, cm^{-1}: 1665, 1565. ^{1}H NMR spectrum, δ, ppm: 2.66 s (3H, CH$_3$), 3.78 d (2H, CH$_2$, *J* = 16.8 Hz), 4.02 d (2H, CH$_2$, *J* = 16.8 Hz), 13.8 br.s (1H, OH). Found, %: C 44.57; H 4.35; S 17.18. $[M]^+$ 188. $C_7H_8O_4S$. Calculated, %: C 44.67; H 4.28; S 17.04.

Compounds **VIIa** and **VIIb** were synthesized from sulfoxide **VI** by the procedure described above for the synthesis of enamines **V**.

4-(1-Allylaminoethylidene)-2*H*-1λ^4-thiopyran-3,5(4*H*,6*H*)-dione 1-oxide (VIIa). Yield 0.18 g (79%), mp 137–138°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 1650, 1590, 1470, 1430, 1420, 1375, 1360, 1340, 1300, 1270, 1210, 1120, 1110, 1045, 950, 905. ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH$_3$), 3.72 d (2H, CH$_2$, *J* = 18.0 Hz), 3.90 d (2H, CH$_2$, *J* = 18.0 Hz), 4.12 m (2H, CH$_2$), 5.30 m (2H, CH$_2$=), 5.90 m (1H, CH=), 13.34 br.s (1H, NH). Found, %: C 53.07; H 5.95; N 6.01; S 14.18. $[M]^+$ 227. $C_{10}H_{13}NO_3S$. Calculated, %: C 52.85; H 5.77; N 6.16; S 14.11.

4-[1-(4-Methoxyphenylamino)ethylidene]-2*H*-1λ^4-thiopyran-3,5(4*H*,6*H*)-dione 1-oxide (VIIb). Yield 0.21 g (72%), mp 168°C (decomp.; from ethyl acetate). IR spectrum, ν, cm^{-1}: 1650, 1620, 1590, 1580. ^{1}H NMR spectrum, δ, ppm: 2.52 s (3H, CH$_3$), 3.78 d (2H, CH$_2$, *J* = 16.0 Hz), 3.88 s (3H, OCH$_3$), 3.96 d (2H, CH$_2$, *J* = 16.0 Hz), 7.02 m (4H, H$_{arom}$), 14.6 br.s (1H, NH). Found, %: C 57.17; H 5.24; N 4.85; S 11.01. $[M]^+$ 293. $C_{14}H_{15}NO_4S$. Calculated, %: C 57.32; H 5.15; N 4.77; S 10.93.

REFERENCES

1. UK Patent no. 2 202 529, 1988; *Chem. Abstr.,* 1989, vol. 110, mo. 114 681.
2. JPN Patent no. 62-298 584, 1986; *Chem. Abstr.,* 1988, vol. 109, no. 68 850.
3. PCT WO Int. Patent Appl. no. 9 931 037, 1999; *Chem. Abstr.,* 1999, vol. 131, no. 44 848.

4. US Patent no. 6 191 140, 1999; *Chem. Abstr.,* 2001, vol. 134, no. 178 542.
5. Terasawa, T. and Okada, T., *Steroids,* 1981, vol. 37, p. 445.
6. Budnikova, M.V., Lis, L.G., and Mikhal'chuk, A.L., *Russ. J. Gen. Chem.,* 1999, vol. 69, p. 1012.
7. Budnikova, M.V., Zheldakova, T.A., Rubinov, D.B., and Mikhal'chuk, A.L., *Russ. J. Org. Chem.,* 2001, vol. 37, p. 293.
8. Terasawa, T. and Okada, T., *J. Org. Chem.,* 1977, vol. 42, p. 1163.
9. Rubinov, D.B., Rubinova, I.L., and Akhrem, A.A., *Chem. Rev.,* 1999, vol. 99, p. 1047.
10. Fehnel, E.A. and Paul, A.P., *J. Am. Chem. Soc.,* 1955, vol. 77, p. 4241.
11. Lakhvich, F.A., Lis, L.G., Rubinov, D.B., Rubinova, I.L., and Akhrem, A.A., *Zh. Org. Khim.,* 1989, vol. 25, p. 1417.