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ANNELATION OF 3,4-DIHYDROISOQUINOLINES BY 3-ACYL-5,5-DIMETHYLTHIOPYRAN-2,4-DIONES. SYNTHESIS AND PROPERTIES OF 8-AZA-17-THIA-D-HOMOGONA-12,17a-DIONES

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We have used annelation of 3,4-dihydroisoquinolines by 3-acyl-5,5-dimethylthiopyran-2,4-diones to obtain the corresponding 8-aza-17-thia-D-homogonanes, which are novel representatives of heterosteroids. We have studied the tautomerism of 3-acylthiopyran-2,4-diones using NMR spectroscopy and H/D-isotope exchange. We have obtained ^{2}H-isotopomers of 3-acylthiopyran-2,4-diones.

Keywords: 8-aza-17-thia-D-homogonanes, azomethines, 3-acyl-5,5-dimethyltetrahydrothiopyran-2,4-diones, heterosteroids, 3,4-dihydroisoquinolines, Schiff's bases, thiopyrano[3',4':5,6]pyrido[2,1-*a*]-isoquinolines, annelation, [2+4] cyclocondensation.

Among heterocyclic analogs of steroids, the most well known today are the aza analogs, in particular those exhibiting quite valuable properties as inhibitors of 5α-reductase and antiandrogens, 4-aza steroids [1, 2], and also 8-aza steroids, which are of considerable practical and theoretical interest as low molecular weight immunomodulators [3-5]. Studies of the structure–function relations in the 8-aza steroid series have shown [3, 5-7] that by means of structural and functional group transformations, we can change both the direction and the level of their immunomodulating effect. A quite promising approach to controlling the immune activity of 8-aza steroids is to introduce additional heteroatoms into their tetracyclic ring [8]. So far 8,16-diaza- [9], 8-aza-16-oxa- [10], 8-aza-16-thia- [11], 8,17-diaza-D-homo- [12], and 8-aza-17-oxa-D-homogonanes have been synthesized and studied [13]. At the same time, compounds in the 8-aza-17-thia-D-homogonane series have been described only recently [14]. With the aim of expanding the indicated series, we have studied the reaction of 3,4-dihydroisoquinolines **1a-d** with 3-acyl-6,6-dimethylthiopyran-2,4-diones **2a,b**, obtained from 6,6-dimethyltetrahydrothiopyran-2,4-dione (**3**). In this case, it was also important to clarify the effect of the sulfur atom in the ring of the original dione **2** on the activity of the latter in the reaction with compounds **1**. We have established that when 3,4-dihydroisoquinolines **1a,b**, unsubstituted in the 1 position, are boiled in ethanol with diones **2a,b**, the corresponding tetracyclic derivatives **4a-d** are formed: the products of an annelation reaction ([2+4] cyclocondensation) at the C=N bond (Scheme 1). However, we were unable to obtain products of type **3** from 1-methyl-substituted dihydroisoquinolines **1c,d** and the same diones **2a,b**. The data presented

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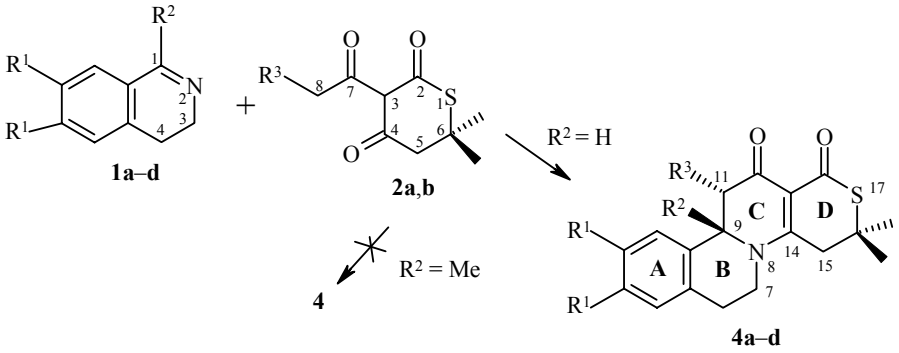
Scheme 1

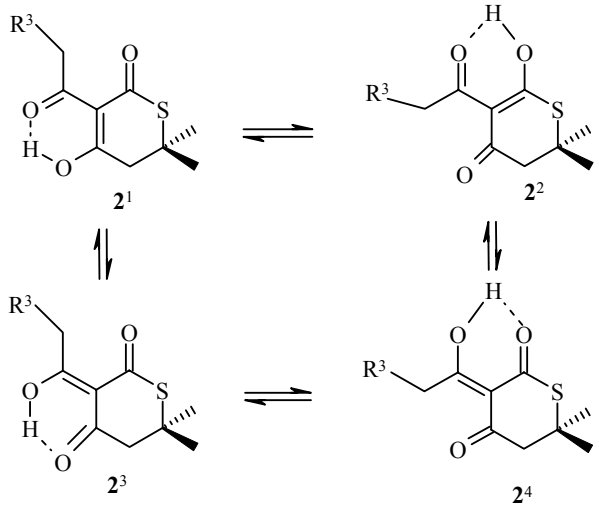


1a,**c**, **4a**,**c** R^1 = H; **1b**,**d**, **4b**,**d** R^1 = OMe; **1a**,**b**, **4a–d** R^2 = H; **1 c**, **d** R^2 = Me;
2a, **4a,b** R^3 = H; **2b**, **4c**,**d** R^3 = Me

along with the results of previous studies [8, 9, 15, 16] allow us to say that in this case, the reaction is hindered by the 1-Me group in dihydroisoquinolines **1c,d** and also by the sulfur atom and the *gem*-dimethyl group in the position 6 of diones **2a,b**.

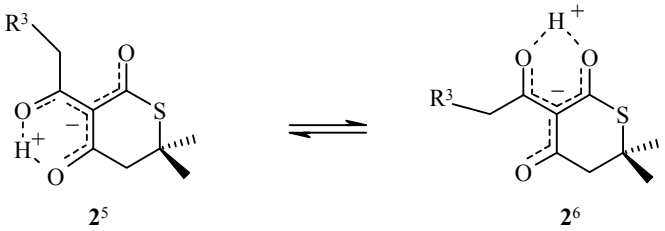
In order for the described reaction to occur, which ultimately involves formation of the $C_{(9)}$–$C_{(11)}$ and $N_{(8)}$–$C_{(14)}$ bonds closing the 2,3-dihydropiperidinone ring **C** of 8-aza-17-thia steroids **4a-d**, both substrates should be at least bifunctionalized. In azomethines **1a-d**, the C=N bond is polarized, and as a result the azomethine carbon atom, which has electrophilic properties, reacts with nucleophiles while the nucleophilic nitrogen atom reacts with electrophiles [17]. According to modern theories, β,β'-tricarbonyl compounds, in particular acylthiopyrandiones **2a,b**, exist as a mixture of interconverting tautomeric *endo*(**2**^{1}, **2**^{2}) and *exo* (**2**^{3}, **2**^{4}) enols (Scheme 2) [18, 19], for which we may expect the presence of four sets of resonance signals in the ^{1}H NMR spectrum. However, due to the low population of individual tautomers, rapid interconversion between them, and other factors, the actually observed number of signals is generally significantly lower. Thus in the ^{1}H NMR spectrum of compound **2a**, along with the four major signals (integrated intensity 93%), there are additional signals at 17.06 ppm and 2.82 ppm (*I* = 7%) corresponding to the enol and methylene protons of the $C_{(5)}H_2$ group respectively.

Scheme 2



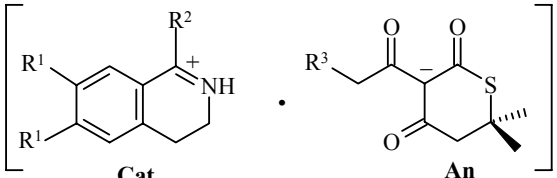
This may be either a consequence of significantly faster interconversion rates between the *endo* and *exo* enols $\mathbf{2}^1 \leftrightarrow \mathbf{2}^3$ and $\mathbf{2}^2 \leftrightarrow \mathbf{2}^4$ than can be distinguished on the NMR time scale [18], or else the tautomers $\mathbf{2}^1$, $\mathbf{2}^3$ and $\mathbf{2}^2$, $\mathbf{2}^4$ degenerate to betaine chelate complexes **2**5 and **2**6 due to 1,5(O,O')-tunneling proton transfer [20]. According to the data in [21], the indicated major signals are assigned to the complex $\mathbf{2}^5$ while the minor signals are assigned to the complex $\mathbf{2}^6$. However, we cannot explain the nucleophilicity of the acyl group in the acylthiopyran diones **2a,b** within such a theory [18].

Scheme 3



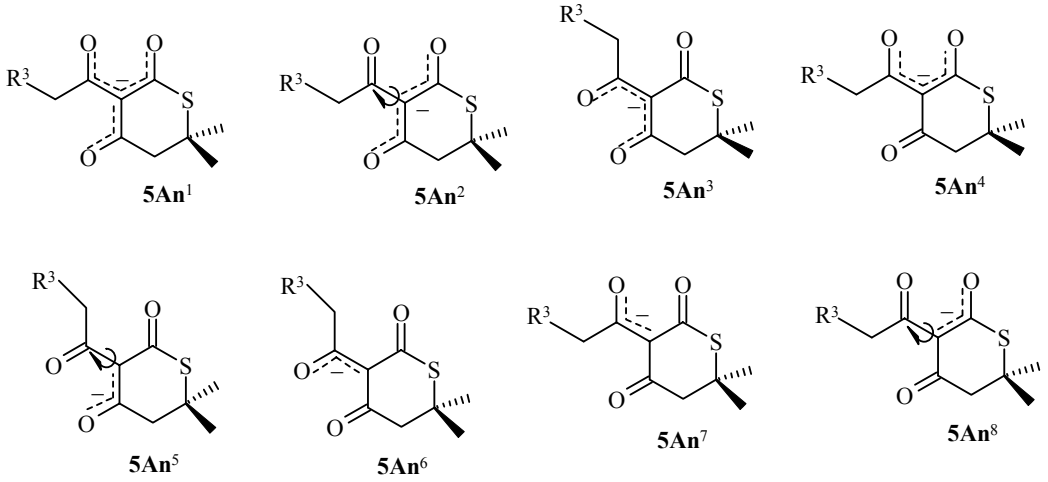
$\mathbf{2}^5$ $\mathbf{2}^6$

Azomethines **1a-d** are bases [22], while the β,β'-tricarbonyl compounds **2a,b** are acids [23]. Consequently, the initial event in their reaction is formation of the salt **5**.



Cat **5** **An**

The mesomeric azomethine cation **5Cat**, as was shown earlier in [15], exists as an equilibrium mixture of immonium and enammonium tautomers. The acylthiopyrandione anion **5An** is also mesomeric, and hypothetically can exist as a heptad mesomer $\mathbf{5An}^1$, pentad mesomers $\mathbf{5An}^2$-$\mathbf{5An}^4$, or triad mesomers $\mathbf{5An}^5$-$\mathbf{5An}^8$.



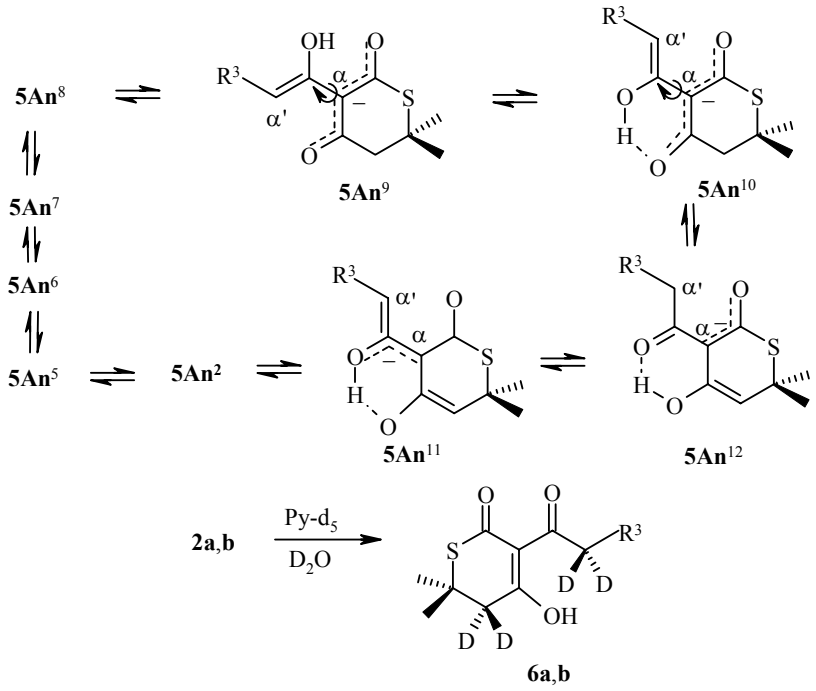
$\mathbf{5An}^1$ $\mathbf{5An}^2$ $\mathbf{5An}^3$ $\mathbf{5An}^4$

$\mathbf{5An}^5$ $\mathbf{5An}^6$ $\mathbf{5An}^7$ $\mathbf{5An}^8$

Due to structural (planarity) and conformational factors, the mesomeric anions **5An**^{2}, **5An**^{5}, and **5An**^{8}, which permit free rotation of the acyl side chain, probably have the highest populations in this series. An isotope exchange study for acetylthiopyrandione **2a** in $CDCl_3$ and Py-d_5 in the presence of D_2O at 20°C showed that under neutral conditions ($CDCl_3$), H/D isotope exchange occurs only for the chelated proton of the enol, while under basic conditions (Py-d_5) such exchange also occurs for the protons of the methyl (methylene) group of the acyl side chain and the methylene group $C_{(5)}H_2$. This suggests that for anions **5**, as for anions of 2-acylcycloalkane-1,3-diones [15, 24, 25] and anions of 3-acylthiotetronic acids [16], a tautomeric equilibrium is established between the forms [**5An**^{2}, **5An**^{5}-**5An**^{8}] and [**5An**^{9}-**5An**^{12}], where both the α' protons of the acyl substituents and the protons of the $C_{(5)}H_2$ groups are involved in H/D isotope exchange (Scheme 4). The physicochemical characteristics (^{1}H NMR, ^{13}C NMR, and mass spectra) of the 2H-isotopomers **6a,b** obtained are given in the experimental section.

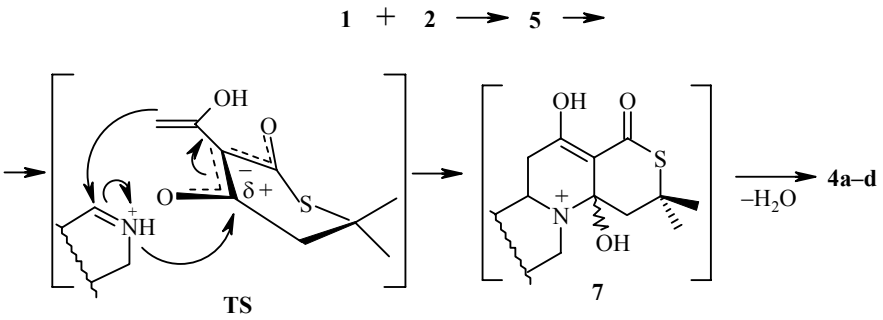
According to ^{1}H NMR data, as a result of H/D isotope exchange for the acylthiopyrandiones **2a,b** in Py-d_5 (D_2O) solutions, H/D isotope exchange also occurs for the chelated enol proton, which during separation of the isotopomers is regenerated due to D/H exchange with atmospheric moisture. As a result, we cannot obtain isotopomers with a chelated deuterium isotope under the described experimental conditions. Analysis of the physicochemical characteristics of ^{2}H isotopomers **6a,b** suggests that their isotopic frequency is ~90%.

Scheme 4



In light of these data and the theories, we can understand the mechanism for the appearance of nucleophilicity in the α' position of the acylthiopyrandiones **2a,b**, and the electrophilicity of the $C_{(4)}$ atom in the tautomers **5An**^{2}, **5An**^{5}-**5An**^{12} is obvious as a consequence of polarization and alternation effects. Considering the above discussion, the mechanism of the reaction of annelation of 3,4-dihydroisoquinolines **1a-d** by acylthiopyrandiones **2a,b** can be represented by Scheme 5.

Scheme 5



The proposed mechanism, in contrast to what has been discussed earlier in [9, 10, 12] and in accordance with the studies in [11], assumes concerted formation of the C–C and C=N bonds, closing the dihydro-γ-pyridinone ring **C** of product **4** *via* a six-membered transition state **TS**. The hypothetical alcohol **6** is either metastable and dehydrated to form the end product under the reaction conditions, or else it is generally not formed as an intermediate but rather the conversion **5** → **3a-d** occurs with elimination of a water molecule directly during formation of the pyridone ring **C**. Considering the data in [26], the second route is preferred.

The composition and structure of the synthesized compounds **2a,b** and **4a-d** are supported by elemental analysis data and physicochemical studies. Thus in the mass spectra of azathia steroids **4b-d**, there are characteristic sets of signals corresponding to radical molecular ions with mass numbers from [M+2] to [M-2], and also split signals (typical od sulfur-containing compounds) that involve the sulfur atom of the radical ions formed upon fragmentation of the molecular ions.

In the IR spectra of diones **2a,b** there are strong (~80-90%) broadened and asymmetric absorption bands at ~1630, ~1570, and ~1470 cm^{-1} that are due to vibrations of the enolized β,β'-tricarbonyl moiety [19]. The bands at ~1630 cm^{-1} have quite extended high-frequency slopes going into the ~1800 cm^{-1} region, suggesting that they have a complex composition. We may assume that they include absorption bands for symmetric and asymmetric stretching, bending and other vibrations of the C=O groups of the β,β'-tricarbonyl moiety. The bands at ~1570 can be assigned to vibrations of the C=C bonds, while the intense and asymmetric absorption bands in the 1500-1300 cm^{-1} region can be assigned to bending vibrations of the C–H bonds in the methylene and methyl groups adjacent to the β,β'-tricarbonyl moiety. A distinguishing feature of the IR spectra of derivatives **2a,b** is the presence of intense absorption bands in the 870 cm^{-1} region, probably due to stretching vibrations of the C–S bonds.

For the IR spectra of derivatives **4a-d**, characteristic features are the strong broadened and asymmetric absorption bands at ~1680 cm^{-1}, which obviously include absorption bands for stretching vibrations of the CO and C(O)S groups, and bands at ~1530 cm^{-1} due to stretching vibrations of the C=C bond of the enolized β,β'-tricarbonyl moiety [27]. Intense absorption bands in the 1500-1300 cm^{-1} region probably belong to bending vibrations of the C–H bonds of the methylene groups, while the bands in the 800-700 cm^{-1} region probably belong to vibrations of the C–N bond.

In contrast to the cycloalkane-1,3-diones in [19], in the electronic absorption spectra of 3-acylthiopyran-2,4-diones **2a,b** we observe three absorption bands, where two long-wavelength absorption bands (240-320 nm) have well-resolved maxima and the short-wavelength absorption band (210-240 nm) has a pronounced absorption maximum in the case of derivative **2a** while in the case of derivative **2b** it appears as a faint shoulder on the high-frequency slope of the spectral line. The refined values for the absorption maxima and minima for diones **2a,b** (obtained by taking the derivatives of the experimental spectral lines) are: for acetylthiopyrandione **2a**, λ_{max} 225, 255, and 285 nm; λ_{min} 207.7, 240, 269.6, and 303.1 nm; for propionylthiopyrandione **2b**, λ_{max} 226.2, 255.4, 285.4, and 418.9 nm; λ_{min} 210.4, 242.3, 270, 303.9, 404.6, and 440 nm. While the numerical values for the two intense ($\log \varepsilon > 4$) long-wavelength absorption bands correlate well with the absorption bands

observed for alicyclic β,β'-tricarbonyl compounds in [19] and consequently can be assigned to $\pi \rightarrow \pi^*$ electronic transitions in the β,β'-tricarbonyl moiety, the short-wavelength absorption band may be due to the sulfur atom present in the structure of these compounds and probably can be assigned to electronic transitions in the thiolactone group. In addition to the absorption bands discussed above, for compound **2b** we can observe very broad (~60-100 nm) low-intensity absorption bands ($\varepsilon < 100$) in the long-wavelength region of the spectrum that are due to $n \rightarrow \pi^*$ electronic transitions.

In the electronic absorption spectra of azathia-D-homogonanes **4a,c**, there are two intense absorption bands ($\log \varepsilon > 4$) at ~270 nm and ~315 nm that are typical of compounds containing an α-acyl-β-aminovinylcarbonyl (AAVC) group $N_{(8)}–C_{(14)}=C_{(13)}(–C_{(12)}=O)–C_{(17/17a)}=O$ [5, 11, 12]. In the spectra of derivatives **4b,d**, along with what has been indicated, there are also asymmetric absorption bands in the ~230 nm region (of about the same intensity), probably due to electronic transitions of the methoxy-substituted aromatic ring **A** [5, 12, 13] and the thiolactone moiety. Evidence in favor of such a conclusion is the fact that the intensity of absorption bands due to only the methoxy-substituted aromatic ring **A** is generally significantly lower [5, 12, 13].

The NMR data were the most informative for the structural studies. Thus in the ^{1}H NMR spectra of compounds **4a-d**, there are resonance signals from all the protons of the proposed structures, with a characteristic pattern of spin–spin couplings revealed using the double resonance method. The position of the sulfur atom in products **4** was established based on analysis of long-range spin–spin couplings, showing that for all the indicated compounds, we observe a direct and a reverse NOE (nuclear Overhauser effect) for protons in the positions 7 and 15, which clearly confirms position 15 for the methylene unit and accordingly position 17 for the sulfur atom.

The series of homogonane diones **4a-d** obtained also provided the opportunity to observe and study the individual and combined effect on the spectral characteristics of these compounds from the methoxy substituents on the aromatic ring **A** and the methyl group on the pyridine ring **C.** The effect of the methoxy group on the benzyl proton H-9 is worth noting: it is expressed in a 20-40 Hz upfield shift of the signal from the latter (diones **4b,d**). It may be due either to a hyperconjugation effect [17] or to stereoelectronic interactions between the indicated proton and the π-electron cloud of ring **A** through space. We can easily track the effect of the 11-CH_3 group from the downfield shift we see in all cases for the signal from the equatorial proton H-7. This effect can be explained by perturbation of the planarity of the aminovinyldicarbonyl moiety. The remaining ^{1}H signals for compounds **4a-d** are found in regions typical for spectra of 8-aza-D-homogonanes [19, 21, 26].

The most pronounced differences between the homogonane diones **4a-d** are observed in their ^{13}C NMR spectra. These differences are connected not only with the appearance of additional signals as we go from the unsubstituted dione **4a** to the 2,3-dimethoxy or the 11-methyl derivatives **4b-d**, but also with different positions for some of the ^{13}C atoms common to all the structures. Thus introducing OMe electron-donor substituents onto the aromatic ring **A** causes quite obvious changes in the multiplicity and position of the signals for the ^{13}C atoms forming it, while substitution of the proton in the 11-CH_2 group by a methyl substituent leads to a change in the multiplicity and position of the $^{13}C_{(11)}$ signal. However, the shifts of signals for nuclei far away from the positions where structural changes occur are more meaningful for studying and understanding the stereoelectronic changes in the molecules of the considered series of compounds. Thus the 11-methyl derivatives **4c,d** differ from their 11-unsubstituted analogs **4a,b** in the signals for the $^{13}C_{(9)}$, $^{13}C_{(7)}$, $^{13}C_{(13)}$ atoms that are shifted downfield by ~4.0 ppm, 1.0 ppm, and 1.5 ppm respectively, and also in the signal for the $^{13}C_{(12)}$ atom, which is found ~3 ppm upfield. These shifts are certainly connected with differences in the electronic environment of the indicated atoms, and those differences in turn are connected with a change in the planarity of the AAVC moiety. The change in the planarity of the AAVC moiety when a methyl group is introduced into the position 11 may be explained by stereoelectronic effects involving interaction of the group with the π-electrons of the aromatic ring **A**. This conclusion is quite consistent with X-ray diffraction data for 8-aza steroids [28] and

the results of examination of Dreiding models for compounds **4a-d**, which shows that due to bending of the molecular frameworks at the $N_{(8)}$–$C_{(9)}$ bond, the 11-Me group is found in a region of anisotropy of the π-electron cloud of ring **A**.

Thus as a result of our studies we have established that reaction of 3,4-dihydroisoquinolines **1a,b** with acylthiopyrandiones **2a,b** leads to the previously unknown 8-aza-17-thia-D-homogona-12,17a-diones **4a-d**. Products of annelation with an angular 9-Me group are not formed from 3,4-dihydroisoquinolines **1c,d** and acylthiopyrandiones **2a,b**; the reaction mixtures become tarry and the original substrates cannot be recovered. Attempts to obtain salts **5** from 3,4-dihydroisoquinolines **1c,d** and acylthiopyrandiones **2a,b** remained unsuccessful, which is probably connected with the lability of the latter. We have shown that anions of acylthiopyrandiones **5An** exist as an equilibrium mixture of "enol–anion tautomers" **5An**^{9}-**5An**^{12}, where the tautomerism involves the hydrogen atoms of the methylene (methyl) groups adjacent to the β,β'-tricarbonyl moiety. From acylthiopyrandiones **2a,b**, we obtained ^{2}H-isotopomers **6a,b**, which are of interest for physicochemical and biological studies.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 in KBr disks. The UV spectra were taken on a Specord M-400 spectrophotometer in ethanol. The derivatives of the experimental spectral curves were taken using the built-in software of the instrument. The mass spectra of derivatives **2a,b** and their isotopomers **6a,b** were measured on an HP 5890/5972 GC/MS chromatograph/mass spectrometer (quartz capillary column HP 5MS 30 m × 0.25 mm × 0.25 μm; carrier gas, helium, 0.7-1 μl/min; vaporizer temperature, 250°C; temperature program 40-300°C, 6°C/min). The mass spectra of the azathia steroids **4b-d** were taken on a high-resolution MicroMass MasSpec mass spectrometer with direct injection of the sample and electron ionizing energy 70 eV. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 (^{1}H, 200 MHz and ^{13}C, 50 MHz) and a Bruker DRX-500 (^{1}H, 500 MHz and ^{13}C, 125 MHz) rf spectrometer, internal standard TMS.

The course of the reactions was monitored using TLC on Silufol UV-254 plates, eluent 9:1 chloroform–methanol. The melting points were determined on a Boetius heating stage.

The 3,4-dihydroisoquinolines **1a-d** used in this work were obtained by cyclodehydration of the corresponding phenethylamides when treated with PPA (azomethines **1a,b**) or phosphorus oxychloride (azomethines **1c,d**) under Bischler–Napieralski reaction conditions [29]. 3-Acylthiopyran-2,4-diones **2a,b** were obtained by acylation of thiopyrandione **3** [30] by acetyl and propionyl chlorides in the presence of pyridine, followed by Claisen–Haase O,C-isomerization [29] of the enol acylates formed as intermediates by treatment with 4-dimethylaminopyridine [31]. Since 3-acylthiopyran-3,4-diones **2a,b** have been described only in patent literature [31], where there are no details given for the synthesis and their physicochemical characteristics are not indicated, we considered it advisable to give the general procedure for obtaining these compounds and data from physical and chemical investigation methods.

3-Acyl-6,6-dimethyltetrahydro-2H-thiopyran-2,4-diones (2a,b) (General Procedure). Dry pyridine (0.97 ml, 12 mmol) and the corresponding acid chloride (11 mmol) were added while stirring to thiopyrandione **3** (1.58 g, 10 mmol) in dry toluene (40 ml). The reaction mixture was stirred for 1 h (monitored by TLC, visualized with an iron chloride solution). Then the reaction mixture was washed with a 1% HCl solution, water, and a Na_2CO_3 solution; then it was dried with Na_2SO_4 and filtered. Dimethylaminopyridine (0.25 g, 2 mmol) was added to the filtrate; the mixture was stirred while protected from moisture for 6-8 h (monitored by TLC). The reaction mixture was extracted with a 10% NaOH solution until the β-triketone **2** was completely recovered (extract 1). Extract 1 was acidified with a 10% HCl solution and extracted with chloroform (4 × 20 ml, extracts 2). The combined extracts 2 were dried with Na_2SO_4 and then filtered. The filtrate was evaporated down on a rotary evaporator and the residue was crystallized from ether.

3-Acetyl-6,6-dimethyltetrahydro-2H-thiopyran-2,4-dione (2a). Dione **2a** (1.32 g) was obtained as cream-colored crystals from thiopyrandione **3** (1.58 g, 10 mmol) [30] and acetyl chloride (0.78 ml, 11 mmol). Yield 66%; mp 100°C (ether). IR spectrum, ν, cm^{-1}: 3450, 1630, 1560, 1545, 1450, 1420, 1395, 1370, 1325, 1295, 1260, 1240, 1205, 1160, 1130, 1115, 1045, 1030, 985, 935, 880. UV spectrum, λmax, nm (lg ε): 229.6 (4.02), 256.6 (4.05), 280.4 (4.07); λ_{min}, nm (log ε): 240 (4.00), 267.3 (4.03). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.50 (6H, s, 6-CH_3); 2.58 (3H, s, 8-CH_3); 2.96 (2H, s, 2H-5); 18.40 (1H, s, OH). ^{13}C NMR spectrum (Py-d_5), δ, ppm: 27.616 (C-8); 29.348 (6-CH_3); 42.988 (C-6); 49.791 (C-5); 112.885 (C-3); 189.095 (C-2); 197.226 (C-4); 199.762 (C-7). Mass spectrum, *m*/*z* (I_{rel}, %): 202.05 $[M+2]^{+\cdot}$ (5.8); 201.05 $[M+1]^{+\cdot}$ (11.3); 200.05 $[M]^{+\cdot}$ (100); 185.05 $[M-15]^{+\cdot}$ (15.3); 172.10 (12.1); 167.10 (15.4); 158.05 (3.2); 157.05 (20.0); 153.05 (5.1); 151.05 (6.6); 145.05 (13.5); 144.05 (13.1); 126.00 (10.0); 125.10 (4.3); 115.95 (9.1); 110.95 (7.1); 100.95 (9.0); 99.00 (3.1); 98.00 (50.9); 89.00 (5.9); 24.65 (87.9); 85.00 (19.9); 84.00 (74.3); 83.00 (63.8); 76.95 (3.2); 74.95 (13.9); 73.95 (9.5); 70.95 (3.0); 69.95 (11.5); 68.95 (30.4); 66.95 (5.6); 60.95 (3.3); 58.90 (20.2); 57.90 (3.2); 57.00 (6.6); 56.00 (9.7); 55.00 (21.2); 53.00 (7.2); 45.00 (7.5); 44.00 (5.8); 43.00 (77.6); 42.10 (5.0). Found, %: C 53.79, 53.87; H 5.92, 5.85; S 16.12, 15.84. $C_9H_{12}O_3S$. Calculated, %: C 53.98; H 6.04; S 16.01. M 200.26.

6,6-Dimethyl-3-propionyltetrahydro-2H-thiopyran-2,4-dione (2b). Propionylthiopyrandione **2b** (1.28 g) was obtained as colorless crystals from thiopyrandione **3** (1.58 g, 10 mmol) [30] and propionyl chloride (0.96 ml, 11 mmol). Yield 60%; mp 53°C (ether). IR spectrum, ν, cm^{-1}: 3450, 1630, 1580, 1560, 1450, 1420, 1395, 1370, 1310, 1270, 1260, 1140, 1130, 1085, 985, 940, 870. UV spectrum, λ_{max}, nm (log ε): 257.7 (4.09), 280.8 (4.10), 413.5 (2.51); λ_{min}, nm (log ε): 205 (3.56), 270 (4.07), 365 (2.38). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.0, 9-CH_3); 1.50 (6H, s, two 6-CH_3); 2.90 (2H, s, two H-5); 3.04 (2H, q, *J* = 7.0, two H-8); 18.54 (1H, s, OH). ^{13}C NMR spectrum (Py-d_5), δ, ppm: 8.852 ($C_{(9)}$); 29.301 (6-CH_3); 33.582 ($C_{(8)}$); 43.043 ($C_{(6)}$); 49.391 ($C_{(5)}$); 112.415 ($C_{(3)}$); 188.982 ($C_{(2)}$); 196.402 ($C_{(4)}$); 204.084 ($C_{(7)}$). Mass spectrum, *m*/*z* (I_{rel}, %): 216.10 $[M+2]^{+\cdot}$ (5.77); 215.10 $[M+1]^{+\cdot}$ (12.2); 214.10 $[M]^{+\cdot}$ (98.9); 199.05 $[M-15]^{+\cdot}$ (4.2); 186.05 (4.2); 185.05 (35.6); 182.10 (3.1); 181.10 (28.2); 180.10 (8.0); 172.00 (5.6); 171.10 (11.6); 165.10 (25.7); 158.95 (4.6); 157.95 (6.1); 156.95 (3.6); 153.05 (3.6); 140.00 (7.6); 138.00 (3.2); 130.00 (16.5); 125.00 (9.2); 124.00 (3.9); 116.95 (4.7); 111.95 (19.3); 110.95 (6.4); 101.95 (17.3); 100.95 (6.8); 99.00 (8.9); 98.00 (23.6); 97.00 (14.8); 89.00 (5.9); 86.90 (3.2); 83.00 (100); 76.95 (3.8); 74.95 (14.4); 73.95 (7.7); 70.95 (4.1); 69.95 (5.4); 68.95 (51.6); 66.95 (3.6); 60.95 (5.4); 58.90 (18.1); 57.90 (4.8); 57.00 (67.5); 56.00 (9.5); 55.00 (27.4); 53.00 (8.8); 51.00 (3.1); 45.00 (7.3); 44.00 (5.3); 43.00 (11.8); 42.10 (4.7). Found, %: C 55.87, 55.93; H 6.53, 6.46; S 14.82, 15.05. $C_{10}H_{14}O_3S$. Calculated, %: C 56.05; H 6.59; S 14.96. M 214.28.

***rac*-16,16-Dimethyl-8-aza-17-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-diones (General Procedure).** An equimolar mixture of 3,4-dihydroisoquinoline **1a-d** and acylthiopyrandione **2a,b** in an ~3-5-fold volume of alcohol was boiled under a stream of argon; the course of the reaction was followed using TLC. It took 15-24 h to complete the process. Then the reaction mixture was evaporated down to one-third of the original volume and held at 0 to +5°C. The separated product **4** was filtered out and recrystallized from alcohol.

***rac*-16,16-Dimethyl-8-aza-17-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (4a).** Product **4a** (0.21 g) was obtained as colorless crystals from isoquinoline **1a** (0.13 g, 1 mmol) and dione **2a** (0.2 g, 1 mmol). Yield 67%; mp 227-230°C (alcohol). IR spectrum, ν, cm^{-1}: 3100-2830, 1680, 1620, 1590, 1530, 1500, 1480, 1445, 1420, 1380, 1320, 1300, 1270, 1250, 1230, 1200, 1160, 1150, 1120, 1070, 1040, 1010, 985, 955, 905, 890, 880, 840, 800, 760. UV spectrum, λ_{max}, nm (log ε): 273.80 (4.25), 315.30 (4.35); λ_{min}, nm (log ε): 236.45 (3.77), 288.80 (4.06). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.48 (3H, s, 16-CH_3); 1.52 (3H, s, 16-CH_3); 2.70 (1H, dd, J_1 = 15.0, J_2 = 15.5, 11-H_B); 2.90 (1H, dd, J_1 = 15.5, J_2 = 4.0, 11-H_A); 2.98 (2H, s, two 15-H); 3.02 (2H, m, two 6-H); 3.50 (1H, m, 7-H_a); 4.20 (1H, tt, J_1 = 13.0, $J_{2,3}$ = 4.0, 7-H_e); 5.94 (1H, dd, *J* = 15.0, *J* = 4.0, 9-H_X); 7.20 (4H, m, 1-, 2-, 3-, 4-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.40 (16-CH_3), 29.62 (16-CH_3), 30.14 ($C_{(6)}$), 42.79 ($C_{(11)}$), 43.30 ($C_{(16)}$), 45.94 ($C_{(15)}$), 46.68 ($C_{(7)}$), 57.59 ($C_{(9)}$), 107.98 ($C_{(13)}$), 127.03 ($C_{(4)}$),

128.33 ($C_{(1)}$), 128.46 ($C_{(3)}$), 129.04 ($C_{(2)}$), 132.06 ($C_{(10)}$), 136.11 ($C_{(5)}$), 170.55 ($C_{(14)}$), 189.89 ($C_{(17a)}$), 194.49 ($C_{(12)}$). Found, %: C 69.09, 68.92; H 6.05, 6.20; N 4.38, 4.34; S 10.12, 10.36. $C_{18}H_{19}NO_2S$. Calculated, %: C 68.98; H 6.11, N 4.47; S 10.23. M 313.40.

***rac*-2,3-Dimethoxy-16,16-dimethyl-8-aza-17-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (4b).** Product **4b** (0.264 g) as colorless crystals was obtained from isoquinoline **1b** (0.19 g, 1 mmol) and dione **2a** (0.2 g, 1 mmol). Yield 70.7%; mp 259-261°C (alcohol). IR spectrum, ν, cm^{-1}: 3100-2830, 1680, 1620, 1600, 1525, 1510, 1455, 1420, 1380, 1340, 1310, 1265, 1230, 1210, 1150, 1120, 1065, 1055, 1020, 990, 960, 870, 835, 780. UV spectrum, λ_{max}, nm (log ε): 202.4 (4.73), 230.6 (4.14), 275.00 (4.25), 315.30 (4.29); λ_{min}, nm (log ε): 225.05 (4.40), 246.75 (3.90), 292.95 (4.14). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.48 (3H, s, 16-CH_3); 1.52 (3H, s, 16-CH_3); 2.65 (1H, dd, *J* = 15.0, *J* = 15.5, 11-H_B); 2.86 (1H, dd, *J* = 15.5, *J* = 3.5, 11-H_A); 2.89 (1H, m, 6-H_e); 2.96 (2H, s, two 15-H); 3.05 (1H, m, 6-H_a); 3.42 (1H, tt, *J* = 11, *J* = 3.6, 7-H_a); 3.85 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 4.20 (1H, tt, *J* = 13, *J* = 4, 7-H_e); 4.85 (1H, dd, *J* = 15.1, *J* = 3.5, 9-H_X); 6.63 (1H, s, 4-H); 6.68 (1H, s, 1-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.38 (16-CH_3); 29.68 (16-CH_3); 29.80 ($C_{(6)}$); 43.31 ($C_{(16)}$); 43.32 ($C_{(11)}$); 45.86 ($C_{(15)}$); 46.72 ($C_{(7)}$); 56.30 (3-OCH_3); 56.46 (2-OCH_3); 57.85 ($C_{(9)}$); 107.95 ($C_{(13)}$); 110.07 ($C_{(4)}$); 111.95 ($C_{(1)}$); 124.83 ($C_{(10)}$); 128.40 ($C_{(5)}$); 149.40 ($C_{(3)}$); 149.79 ($C_{(2)}$); 170.38 ($C_{(14)}$); 189.79 ($C_{(17a)}$); 194.72 ($C_{(12)}$). Mass spectrum, *m*/*z* (I_{rel}, %): 375 $[M+2]^{+\cdot}$ (8.4), 374 $[M+1]^{+\cdot}$ (25.1), 373 $[M]^{+\cdot}$ (100); $[M-1]^{+\cdot}$ 372 (13.3), 359 (7.2), 358 $[M-15]^{+\cdot}$ (27.4), 346 (9.1), 345 (40.8), 341 (12.5), 340 (45.5), 331 (12.5), 330 (33.0), 313 (8.5), 312 (16.5), 302 (11.5), 299 (14.8), 298 (39.5), 284 (12.3), 271 (18.8), 270 (24.5), 256 (6.3), 243 (17.9), 242 (16.5), 204 (8.3), 192 (8.1), 191 (13.7), 190 (30.0), 188 (10.5), 177 (8.1), 176 (12.3), 146 (8.5), 115 (5.0), 107 (7.5), 91 (5.5), 77 (9.5), 59 (8.5). Found: *m*/*z* 373.133661 $[M]^{+\cdot}$ $C_{20}H_{23}NO_4S$. Calculated: M 373.134780.

***rac*-11,16,16-Trimethyl-8-aza-17-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (4c).** Product **4c** (0.25 g) was obtained as colorless crystals from isoquinoline **1a** (0.13 g, 1 mmol) and dione **2b** (0.21 g, 1 mmol). Yield 77%; mp 223-225°C (alcohol). IR spectrum, ν, cm^{-1}: 3100-2830, 1680, 1600, 1530, 1505, 1475, 1450, 1380, 1360, 1320, 1300, 1270, 1265, 1240, 1200, 1150, 1130, 1110, 1060, 1030, 1010, 990, 970, 940, 885, 835, 800, 760. UV spectrum, λ_{max}, nm (log ε): 273.25 (4.26), 315.00 (3.36); λ_{min} nm (log ε): 237.35 (3.82), 288.55 (4.06). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.82 (3H, d, 11-CH_3); 1.48 (3H, s, 16-CH_3); 1.52 (3H, s, 16-CH_3); 2.68 (1H, m, 11-H); 3.02 (4H, m, two H-15, two 6-H); 3.40 (1H, m, 7-H_a); 4.32 (1H, m, 7-H_e); 5.04 (1H, d, *J* = 2.7, 9-H_a); 7.26 (4H, m, 1-, 2-, 3-, 4-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.46 (11-CH_3), 29.39 (16-CH_3), 29.63 (16-CH_3), 30.09 ($C_{(6)}$), 43.24 ($C_{(16)}$), 46.79 ($C_{(15)}$), 47.61 ($C_{(7)}$), 49.51 ($C_{(11)}$), 61.68 ($C_{(9)}$), 109.46 ($C_{(13)}$), 125.53 ($C_{(3)}$), 126.78 ($C_{(4)}$), 129.29 ($C_{(1)}$), 129.10 ($C_{(2)}$), 134.76 ($C_{(10)}$), 135.24 ($C_{(5)}$), 171.40 ($C_{(14)}$), 188.79 ($C_{(17a)}$), 189.94 ($C_{(12)}$). Mass spectrum, *m*/*z* (I_{rel}, %): 329 $[M+2]^{+\cdot}$ (9.8), 328 $[M+1]^{+\cdot}$ (31.9), 327 $[M]^{+}$ (100), 326 $[M-1]^{+\cdot}$ (9.0), 325 $[M-2]^{+\cdot}$ (5.5), 313 (11.6), 312 $[M-15]^{+\cdot}$ (41.5), 299 (19.5), 298 (6.0), 296 (6.5), 295 (12.0), 294 (48.9), 285 (9.5), 284 (24.7), 278 (7.0), 267 (6.1), 266 (12.0), 253 (11.5), 252 (29.1), 238 (8.5), 225 (7.8), 224 (12.6), 209 (5.8), 210 (7.6), 197 (13.1), 196 (20.5), 182 (10.2), 181 (8.6), 132 (26.5), 131 (10.1), 130 (35.9), 129 (8.9), 128 (12), 117 (11.9), 116 (8.6), 115 (15.8), 108 (9.8), 106 (5.5), 105 (6.4), 103 (7.4), 91 (9.2), 77 (12.8), 59 (8.5). Found: *m*/*z* 327.129547 $[M]^{+\cdot}$ $C_{19}H_{21}NO_2S$. Calculated: M 327.129301.

***rac*-2,3-Dimethoxy-11,16,16-trimethyl-8-aza-17-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (4d).** Product **4c** (0.29 g) as colorless crystals was obtained from isoquinoline **1b** (0.19 g, 1 mmol) and dione **2b** (0.21 g, 1 mmol). Yield 72%; mp 268-270°C (alcohol). IR spectrum, ν, cm^{-1}: 3100-2830, 1685, 1660, 1620, 1600, 1520, 1460, 1450, 1380, 1360, 1340, 1320, 1310, 1270, 1235, 1210, 1155, 1130, 1110, 1085, 1040, 1025, 995, 940, 880, 825, 795. UV spectrum, λ_{max}, nm (log ε): 202.35 (4.55), 231.45 (4.09), 275.00 (4.18), 314.40 (4.22); λ_{min}, nm (log ε): 222.05 (4.05), 247.05 (3.85), 290.00 (4.09). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.8 (3H, d, *J* = 7, 11-CH_3); 1.47 (3H, s, 16-CH_3); 1.51 (3H, s, 16-CH_3); 2.62 (1H, m, 11-H_a); 2.86 (1H, dd, J_1 = 15.6, J_2 = 2.8, 11-H_a); 2.96 (4H, m, two 6-H, two 15-H); 3.34 (1H, ddd, $J_{1,2}$ = 12.4, J_3 = 2.3, 7-H_a); 3.85 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 4.30 (1H, tt, J_1 = 12.4, $J_{2,3}$ = 2.3, 7-H_e);4.96 (1H, d, 9-H_a); 6.58 (1H, s, 4-H);

6.67 (1H, s, 1-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.51 (11-CH_3), 29.41 (16-CH_3), 29.59 (16-CH_3), 29.75 ($C_{(6)}$), 43.36 ($C_{(16)}$), 45.02 ($C_{(15)}$), 47.52 ($C_{(11)}$), 47.68 ($C_{(7)}$), 56.51 (2-OCH_3), 56.34 (3-OCH_3), 61.87 ($C_{(9)}$, 109.54 ($C_{(13)}$), 110.29 ($C_{(4)}$), 112.32 ($C_{(1)}$), 126.78 ($C_{(10)}$), 127.44 ($C_{(5)}$), 149.57 ($C_{(2)}$), 149.57 ($C_{(3)}$), 174.41 ($C_{(14)}$), 189.18 ($C_{(17a)}$), 190.41 ($C_{(12)}$). Mass spectrum, *m*/*z* (I_{rel}, %): 390 $[M+2]^{+\cdot}$ (8.0), 388 $[M+1]^{+\cdot}$ (26.5), 387 $[M]^{+\cdot}$ (100), 386 $[M-1]^{+\cdot}$ (13.0), 373 $[M-2]^{+\cdot}$ (6.8), 372 $[M-15]^{+\cdot}$ (26.8), 359 (8.7), 355 (7.2), 354 (26.5), 350 (8.5), 349 (24.5), 326 (7.2), 312 (11.5), 285 (6.0), 284 (9.0), 270 (5.1) 266 (5.0), 242 (6.2), 192 (13.1), 191 (24.8), 190 (18.8), 177 (8.5), 176 (13.0), 107 (5.8). Found: *m*/*z* 387.147285 $[M]^{+\cdot}$ $C_{21}H_{25}NO_4S$. Calculated: M 387.147058.

[5,5,8,8,8-(5)2H]-3-Acetyl-6,6-dimethyltetrahydro-2H-thiopyran-2,4-dione (6a). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.50 (6H, s, 6-CH_3); 18.6 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.348 (two CH_3); 42.988 ($C_{(6)}$); 112.885 ($C_{(3)}$); 189.095 ($C_{(2)}$); 197.226 ($C_{(4)}$); 199.762 ($C_{(7)}$). Mass spectrum, *m*/*z* (I_{rel},%): 206.20 $[M+1]^{+\cdot}$ (13.2); 295.20 $[M]^{+\cdot}$ (80.9); 204.20 $[M-1]^{+\cdot}$ (64.8); 203.15 (16.6); 190.05 $[M-15]^{+\cdot}$ (10.1); 189.05 (8.4); 177.10 (8.9); 176.10 (7.1); 171.10 (8.5); 179.10 (7.8); 162.05 (16.3); 161.05 (13.6); 148.05 (14.02); 147.05 (18.5); 146.05 (9.0); 131.00 (7.4); 130.00 (7.4); 118.95 (9.5); 117.95 (5.3); 113.95 (5.4); 103.05 (44.4); 102.05 (41.3); 101.05 (12.6); 92.00 (5.1); 91.00 (30.1); 90.00 (15.9); 89.00 (9.6); 88.00 (18.6); 87.00 (82.4); 86.00 (44.6); 85.00 (18.9); 84.00 (84.3); 83.00 (17.4); 74.95 (30.8); 73.95 (23.1); 72.95 (6.1); 69.95 (16.4); 68.95 (42.2); 67.95 (5.7); 60.95 (5.2); 59.95 (6.0); 58.90 (39.5); 58.00 (20.2); 57.00 (21.3); 56.00 (14.1); 55.00 (5.6); 54.00 (6.0); 47.00 (5.1); 46.00 (100); 45.00 (69.5); 44.00 (23.4); 43.00 (14.4); 42.00 (12.7).

[5,5,8,8-(4)2H]-6,6-Dimethyl-3-propionyltetrahydro-2H-thiopyran-2,4-dione (6b). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.18 (3H, s, 9-H_3); 1.50 (6H, s, two 6-CH_3); 18.95 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.852 ($C_{(9)}$); 29.301 (two 6-CH_3); 43.043 ($C_{(6)}$); 112.415 ($C_{(3)}$); 188.982 ($C_{(2)}$); 196.402 ($C_{(4)}$); 204.084 ($C_{(7)}$). Mass spectrum, *m*/*z* (I_{rel}, %): 219.10 $[M+1]^{+\cdot}$ (13.0); 218.10 $[M]^{+\cdot}$ (45.6); 217.10 $[M-1]^{+\cdot}$ (37.1); 216.10 (7.0); 188.05 (11.6); 187.05 (22.2); 186.05 (6.4); 184.15 (12.5); 183.10 (11.6); 182.10 (5.6); 175.10 (6.5); 174.00 (8.1); 168.10 (9.3); 167.10 (12.3); 159.95 (5.8); 143.05 (5.0); 132.00 (11.7); 131.00 (10.5); 127.00 (5.7); 126.00 (6.5); 115.95 (9.5); 114.95 (14.9); 113.95 (7.7); 112.95 (6.0); 103.95 (14.3); 102.95 (15.9); 101.95 (8.4); 100.95 (10.7); 100.00 (21.3); 99.00 (24.0); 98.00 (12.5); 91.00 (7.0); 88.00 (6.2); 87.00 (11.7); 86.00 (12.3); 85.00 (24.4); 84.00 (100); 83.00 (24.80); 74.95 (22.2); 73.95 (13.5); 72.95 (5.2); 71.95 (5.1); 70.95 (8.6); 69.95 (20.4); 68.95 (82.4); 67.95 (7.7); 60.95 (8.4); 59.95 (8.2); 59.00 (88.7); 58.00 (68.8); 57.00 (33.9); 56.00 (26.5); 55.00 (12.6); 54.00 (9.2); 53.00 (7.3); 46.00 (6.0); 45.00 (20.1); 44.00 (17.7); 43.00 (24.5); 42.00 (19.8).

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REFERENCES

1. Li Xun, S. M. Singh, and F. Labrie, *J. Med. Chem.*, **38**, 1158 (1995).
2. M. Lourdusamy, J. Cote, S. Laplante, F. Labrie, and S. M. Singh, *Bioorg. Med. Chem.*, **5**, 305 (1997).
3. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and B. B. Kuz'mitskii, *Vestsi AN BSSR, Ser. Khim. Navuk*, No. 6, 81 (1982).
4. A. A. Akhrem, B. B. Kuz'mitskii, F. A. Lakhvich, V. A. Khripach, and Yu. L. Zhuravkov, in: *The Chemistry and Biology of Immunoregulators* [in Russian], Zinatne, Riga (1985), p. 265.
5. N. A. Konoplya, O. V. Gulyakevich, A. L. Mikhal'chuk, and B. B. Kuz'mitskii, *Vestsi AN Belarusi, Ser. Khim. Navuk*, No. 3, 91 (1994).
6. B. B. Kuz'mitskii, I. G. Dad'kov, Yu. L. Zhuravkov, N. A. Konoplya, G. S. Lyubin, A. E. Mashkovich, V. M. Nasek, O. V. Gulyakevich, V. N. Pshenichnyi, and V. A. Khripach, *Vestsi AN BSSR, Ser. Khim. Navuk*, No. 1, 64 (1989).

7. G. S. Lyubin, I. G. Dad'kov, O. V. Gulyakevich, and B. B. Kuz'mitskii, *Vestsi AN BSSR, Ser. Khim. Navuk*, No. 2, 93 (1990).
8. F. A. Lakhvich, L. G. Lis, and A. A. Akhrem, *Usp. Khim.*, **53**, 1014 (1984).
9. V. N. Pshenichnyi, O. F. Lakhvich, and V. A. Khripach, *Vestsi AN BSSR, Ser. Khim. Navuk*, No. 5, 70 (1991).
10. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and V. N. Pshenichnyi, *Zh. Org. Khim.*, **15**, 1396 (1979).
11. M. V. Budnikova, D. B. Rubinov, L. G. Lis, and A. L. Mikhal'chuk, *Mendeleev Commun.*, **5**, 208 (1999).
12. M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1966).
13. A. A. Akhrem, A. M. Moisenkov, and V. A. Krivoruchko, *Izv. Akad. Nauk SSSR*, *Ser. Khim.*, 1302 (1973).
14. M. V. Budnikova, T. A. Zheldakova, D. B. Rubinov, and A. L. Mikhal'chuk, *Zh. Org. Khim.*, **37**, 306 (2001).
15. A. L. Mikhal'chuk, O. V. Gulyakevich, Yu. V. Shklyaev, V. S. Shklyaev, and A. A. Akhrem, *Khim. Geterotsikl. Soedin.*, 681 (1998).
16. M. V. Budnikova, A. L. Mikhal'chuk, and D. B. Rubinov, *Khim. Geterotsikl. Soedin*., 265 (2004).
17. G. Bekker, *Introduction to the Electronic Theory of Organic Reactions* [Russian translation from German by V. M. Potapov], Mir, Moscow (1977), 658 pp.
18. V. I. Minkin, L. P. Olekhnovich, and Yu. A. Zhdanov, *Molecular Design of Tautomeric Systems* [in Russian], Izdat. Rost. Univ., Rostov (1977), 272 pp.
19. A. L. Mikhal'chuk, O. V. Gulyakevich, A. A. Zenyuk, A. V. Korchik, L. G. Lis, V. A. Khripach, L. I. Ukhova, and A. A. Akhrem, *Dokl. Akad. Nauk*, **317**, 1397 (1991).
20. K. H. Grellman and J. S. Stephan, in: *Abstracts, 210th ACS Division of Physical Chemistry National Meeting, Chicago, Illinois, August 20-24 (1995),* Washington, D.C.
21. A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov, and A. A. Akhrem, Khim. Geterotsikl. Soedin., 374 (1993).
22. *Azomethines. Structure, Properties, and Application* [in Russian], Izdat. Rost. Univ., Rostov-na-Donu (1967), p. 293.
23. O. A. Reutov, I. P. Beletskaya, and K. P. Butin, *CH Acids* [in Russian], Nauka, Moscow (1980), 247 pp.
24. A. L. Mikhal'chuk and O. V. Gulyakevich (BY), Belarus Patent Appl. 19990626; Afitsyiny Byuleten. Vynakhodnitstvy, Karystnyya Madeli, Pramyslovyya Uzory, No. 4, 36 (2000).
25. A. L. Mikhal'chuk and O. V. Gulyakevich (BY), Belarus Patent Appl. 19990627; Afitsyiny Byuleten. Vynakhodnitstvy, Karystnyya Madeli, Pramyslovyya Uzory, No. 4, 36 (2000).
26. A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov, and I. L. Rubinova, *Zh. Org. Khim.*, **34**, 956 (1998).
27. A. A. Akhrem, N. A. Borisevich, A. A. Govorova, O. V. Gulyakevich, A. S. Lyakhov, A. L. Mikhal'chuk, I. V. Skornyakov, and G. B. Tolstorozhev, *Zh. Prirodn. Soedin.*, **69**, 303 (2001).
28. O. V. Gulyakevich, I. L. Rubinova, D. B. Rubinov, A. A. Govorova, A. S. Lyakhov, and A. L. Mikhal'chuk, *Mendeleev Commun.*, 208 (1999).
29. K. V. Vatsuro and G. L. Mishchenko, *Name Reactions in Organic Chemistry* [in Russian], Khimiya, Moscow (1976), 528 pp.
30. K. Schweiger, *Monatsh. Chem.*, **113**, 1283 (1982).
31. H.-J. Wroblowsky, J. Stetter, L. Eue, R. R. Schmidt, and H.-J. Santel, Ger. Pat. 3421351; *Chem. Abstr.* **105**:42651 (1986).