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ANNELATION OF 3,4-DIHYDROISOQUINOLINES WITH 3-ACYLTHIOTETRONIC ACIDS: SYNTHESIS AND PROPERTIES OF 8-AZA-16-THIAGONA-12,17-DIONES AND 3,4-DIHYDROISOQUINOLINIUM 3-ACETYLTHIOTETRONATE

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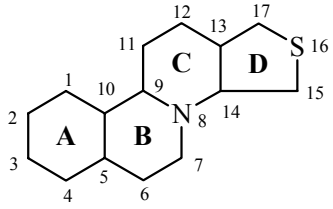
8-Aza-16-thiagona-12,17-diones have been obtained by the annelation of C(1)-unsubstituted 3,4-dihydroisoquinolines with 3-acylthiotetronic acids on refluxing in glacial acetic acid. The condensation of 1-methyl-3,4-dihydroisoquinoline with 3-acetylthiotetronic acid stopped at the salt formation stage. From the results of H/D isotopic exchange of 3,4-dihydroisoquinolinium 3-acetylthiotetronate it follows that a tautomeric equilibrium is established for the anion of 3-acetylthiotetronic acid, involving the protons of the acetyl group and the C(5) methylene group of the thiolactone ring in isotopic exchange.

Keywords: 8-aza-16-thiagona-12,17-diones, 3,4-dihydroisoquinolinium 3-acetylthiotetronate, 3-acylthiotetronic acids, 3,4-dihydroisoquinolines, annelation.

The synthesis of the new heterocyclic system 8-aza-16-thiagonane (benzo[*a*]thieno[*f*]quinolizine) (**1**), which is an ABCD tetracyclic diheteroatom derivative of cyclopentanoperhydrophenanthrene, or gonane, where the carbon atoms in positions 8 and 16 are replaced by atoms of nitrogen and sulfur respectively was reported previously [1,2]. The synthesis of similar compounds pursues two aims: first, the extending of the series of immunomodulators of a heterosteroid nature, such as 8-aza- [3,4], 8-aza-16-oxa- [3,5], and 8,16-diazasteroids [3,6], and secondly, the study of the scope and mechanism of the annelation reactions ([2+4]-cyclocondensation) of cyclic Schiffs' bases by β-di-, β,β'-tricarbonyl compounds, and their enolic derivatives.



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In the present report conditions of synthesis and physicochemical data are given on investigations of 8-aza-16-thiagonanes, and certain conclusions are made regarding the mechanism and scope of the indicated annelation reactions.

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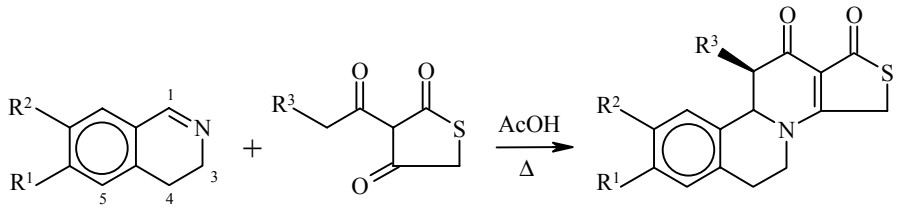
The interaction of 3,4-dihydroisoquinolines **2a-c** with 3-acylthiotetronic acids **3a,b** was effected by refluxing equimolar mixtures of reactants in glacial acetic acid, analogous to the previously described cyclocondensation of compounds **2a-c** with 3-acetyltetronic [5-7] and 3-acetyltetramonic acids [6,8]. The annelation products **4a-d**, as a rule, were isolated from the reaction media as crystalline solids and were purified by recrystallization from trifluoroacetic acid.



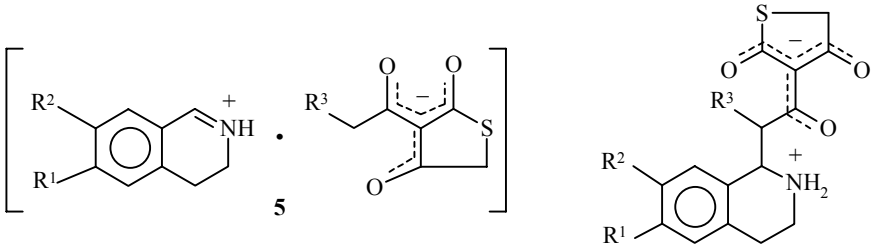
2a–c **3a**,**b** **4a–d**

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

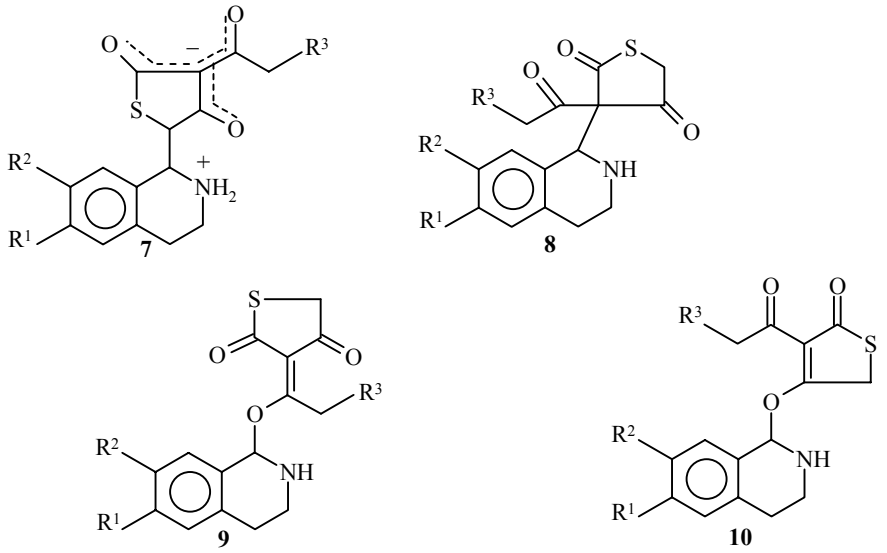
It was confirmed previously [7-10] that on interaction of compounds **2a-c**, displaying the properties of bases, with β,β'-tricarbonyl compounds having an acid nature, in alcohol solutions, salts of type **5** are formed. Our attempts to condense compounds **2a-c** with 3-acetylthiotetronic acids **3a,b** under conditions of kinetic control in order to obtain or even to establish the salt complexes **5,** or the tricyclic adducts of C,C-addition **6** [5-10] postulated for such reactions, were unsuccessful. On refluxing mixtures of the reactants in alcohols difficultly soluble chromatographically heterogeneous crystalline products were isolated from the reaction media and, according to the data of [6-8,10], should be assigned the structure of salts **5**. Separation of the mixtures obtained and isolation of homogeneous compounds were unsuccessful. However a more detailed investigation of these products showed that mostly they are mixtures of mutually converting substances, which hypothetically may be assigned the structure of either salts **5**, or C,C- (**6-8**) or C,O- (**9,10**) adducts [10-12]. Refluxing these substances in acetic acid leads to the desired 8-aza-16-thiagonanes **4a-c.**

In view of the data on prototropy [13,14], and the acid-base and electrophile-nucleophile [12] properties of isoquinolines **2a-c** and 3-acylthiotetronic acids **3a,b**, the salt **5** and adducts **8-10** may be considered as the most likely components of the obtained mixtures. Assumption of the formation of adducts **6** and **7** requires permitting prototropic isomerization conversions of anions of 3-acylthiotetronic acids, which contradicts existing ideas. On the other hand the low solubility of the interaction products in alcohols suggests that structures **5-7** with an ionic character are the most probable for them.

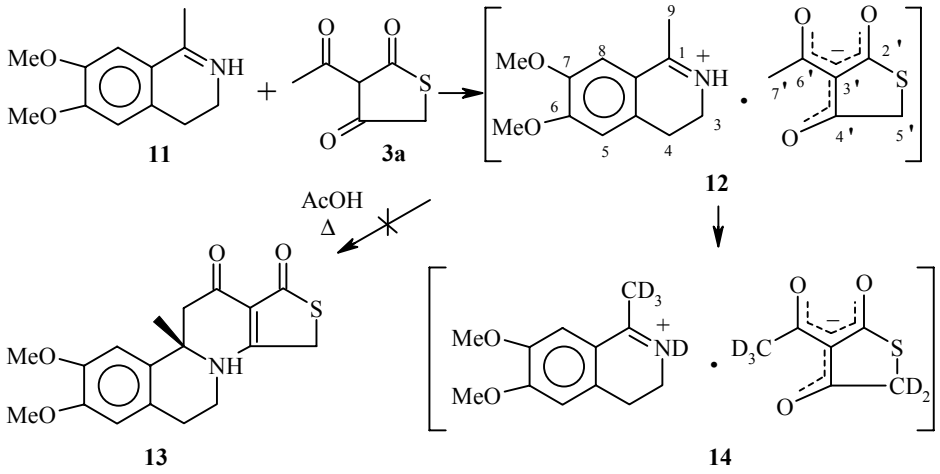
Considering the complexity of identifying the condensation products and also the results of the previously described syntheses of salts of 1-alkyl-3,4-dihydroisoquinolines with 2-acetylcyclopentane-1,3-dione [15,16], it seemed of interest to study the interaction of 3-acetylthiotetronic acid (**3a**) with the 1-methyl-substituted isoquinoline **11**.



5 **6**



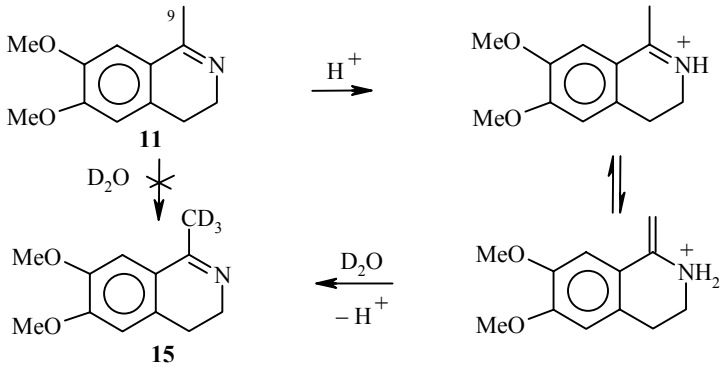
Refluxing an equimolar mixture of these reactants in ethanol for 3-7 h did not lead to the formation of a crystalline product, but TLC data of the reaction mixture (Silufol UV-254, $CHCl_3$–MeOH, 9:1) indicated that the starting materials were unchanged. After adding ether to the reaction mixture and storing at reduced temperature a crystalline substance was isolated, which was assigned the structure of salt **12** on the base of physicochemical data.



Unlike products **4a-d** salt **12** was readily soluble in alcohol, chloroform, water, DMF, and DMSO. Its spectral characteristics corresponded to an ionic form. Attempts to condense salt **12** into the tetracyclic derivative **13** with an angular methyl group in position C(9) by refluxing in glacial acetic acid, as in the case of the salts of 2-acetylcyclopentane-1,3-dione [15,16], did not give the desired result. At the same time the good solubility and stability of salt **12** permitted a detailed study of its properties and comparison of them with the properties of the previously described salts of 1-alkyl-3,4-dihydroisoquinolines with 2-acetylcyclopentane-1,3-dione [16].

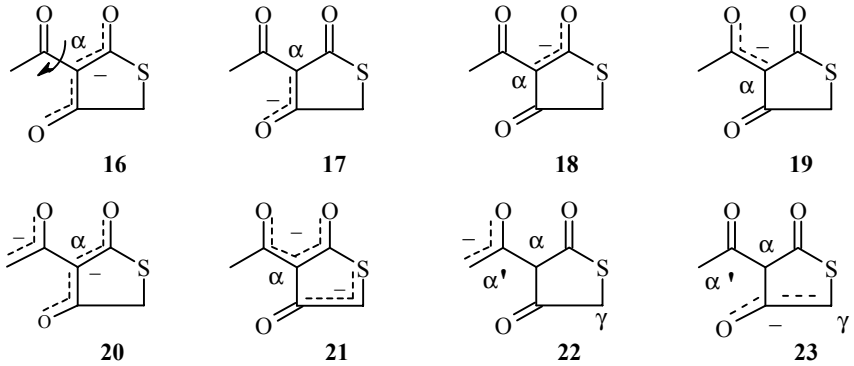
Investigation of the H/D isotopic exchange of salt **12** showed that in addition to the immonium proton the protons of the methyl group of the isoquinolinium ion and all the protons of compound **3a** anion were subjected to isotopic exchange leading to the [2,5',5',7',7',7',9,9,9-(9)-^{2}H]isotopomer **14**. The H/D exchange of the immonium proton is a consequence of its ionic character but the exchange of the methyl group protons of the

isoquinolinium ion is caused by immonium–enammonium tautomerism. It should be mentioned that isotopic exchange for the methyl group of azomethine **11** is not observed in the absence of an acid catalyst even after storing a sample for 20 days in $CDCl_3$ in the presence of D_2O as a deuterium source. In the presence of catalytic amounts (~3-5 mol. %) of toluene-*p*-sulfonic acid or the hydrochloride of azomethine **11** the H/D isotopic exchange of protons of the methyl group was completed, depending on the conditions, in 3-120 h leading to the [9,9,9-(3)-^{2}H]isotopomer **15**. This fact indicates the determining role of the acid catalyst in the tautomerism of 1-alkyl-3,4-dihydroisoquinolines.



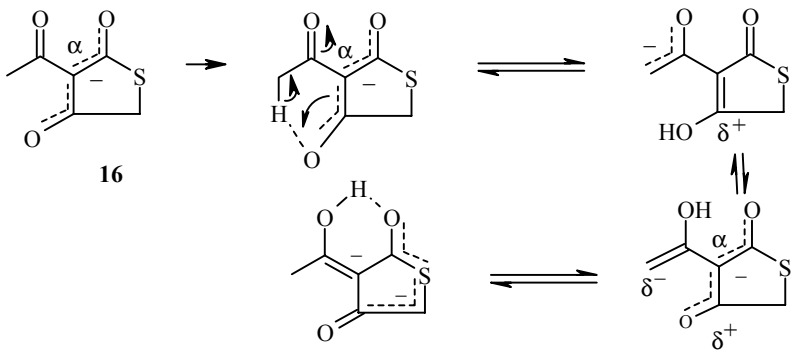
Isotopic exchange of the protons of the methylene group at C(5') and the methyl group of the acetyl substituent of the 3-acetylthiotetronic acid anion in salt **12** proved to be not only unexpected but also contradictory to all the known data and existing ideas on prototropy (tautomerism) of β,β'-tricarbonyl compounds in general and acid **3a** in particular [13,14,16-18]. A separate report will be devoted to a detailed discussion of the results of an investigation of the tautomerism of acids **3a,b** and their derivatives using labeled atoms. It is appropriate here only to make some preliminary remarks on this problem.

According to NMR data it is possible to assign a pentade structure **16** with free rotation of the acetyl group to the mesomeric anion of salt **12** of acid **3a**, together with the heptade structure **12**. At increased temperatures, leading to an increase in the internal energy of the molecules, it is impossible not to consider the possibility of the existence of the theoretically permissible triad structures of type **17-19** for the anion. However none of these structures of the mesomeric α-anions may explain the results of the protium–deuterium exchange nor the mechanism of formation of the cyclocondensation products **4a-d**, assuming the display of 1,4-dipolarophilic properties by acid **3a** or its anion.



The possibility of generating the dianions **20**, **21** or the α'- and γ-anions **22**, **23** under the described reaction conditions as the reason for the observed isotopic exchange is dubious, since it is contradicted both by the properties of the interacting compounds **11** and **3a**, and also by the thermodynamic course of the reaction.

Allowing for this it is possible to assume that a prototropic process (tautomerism) is realized for the anions of acid **3a**, involving the protons of the acetyl substituent and the methylene group at C(5') in the sphere of the H/D isotopic exchange.



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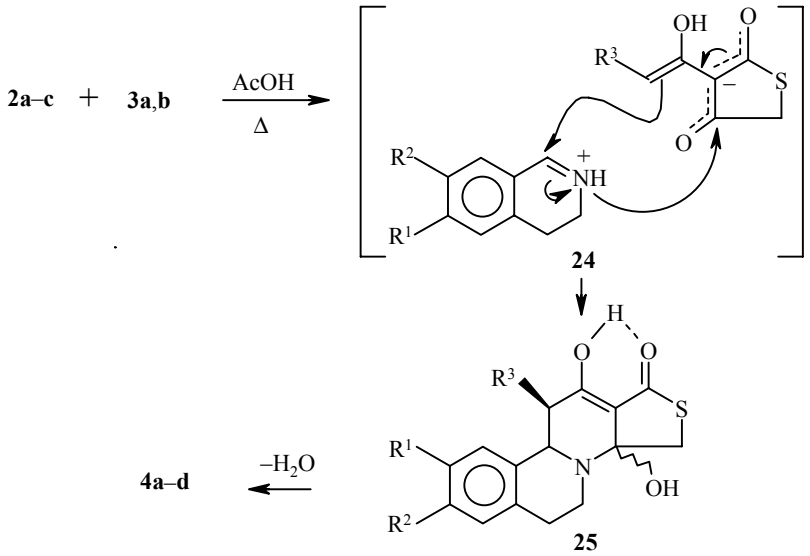
Within the framework of this scheme a thermodynamically possible explanation arises for both the results of the protium–deuterium exchange in the anion of 3-acetylthiotetronic acid and for the 1,4-dipolarophilic properties of these anions on interacting them with azomethines **2a-c** to form annelation products **4a-d**. The results of the H/D isotopic exchange of protons in the anion of salt **12,** together with the data on the solubility of this salt and of the products of the interaction of substrates **2a-c** and **3a,b** in alcohols, suggest that the main components of the mixtures obtained are not salts of type **12** or adducts **8-10** but are compounds **6** and **7** mutually converting from one to the other through salts **5**. The absence of hindrance from the side of the C(1)-alkyl substituents of the isoquinolines **2a-c** on annelation with 2-acetylcyclohexane-1,3-diones [19,20], and the stopping of the reaction in the case of cyclopentane triketones [15,16] and acid **3a**, forced the rejection of the conclusion made above on the course of such reactions through tricyclic adducts of type **6** [10,11], and the assumption in this case of the existence of a concerted mechanism, including the six-membered transition state (**24**) with synchronous formation of C–C and C–N bonds. This process leads to the formation of a metastable tetracyclic derivative **25**, the dehydration of which under the reaction conditions completes the chain of conversions of the starting materials into the final products **4a-d**.



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The obtained 8-aza-16-thiagonanes **4a-d** are less stable than the 8-aza-, 8-aza-D-homo-, 8-aza-16-oxa-, and 8,16-diazagonanes described previously [4,7-10]. Even on storing solutions of these compounds at room temperature, and even more on boiling, significant decomposition was observed (TLC), which is probably caused by the lability of the thiolactone ring D, displaying a tendency towards oxidative, hydrolytic, isomeric, and other conversions. Regretably, establishing the products of such conversions was unsuccessful.

Compounds **4a-c** have high melting points (270-300°C) and, as a rule, melt with decomposition or decompose on reaching the melting point (Table 1). Usually they are intensely colored and luminesce in solution. In the UV spectra of these substances (Table 2) 3-4 absorption bands (AB) are observed. The most short wave AB with a maximum at ~200 nm was observed in some cases only as a shoulder of the band with maximum below 200 nm (for example, for compound **4b**).

TABLE 1. Physicochemical Characteristics of Compounds **4a-d** and **12**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (with dec.)	$[M]^+$	Yield, %
		C	H	N	S			
4a	$C_{15}H_{13}NO_2S$	65.98 66.40	4.56 4.85	4.91 5.16	12.07 12.07	293-295* 320	271.34	78.5*
4b	$C_{16}H_{15}NO_3S$	64.02 63.76	5.11 5.02	4.47 4.65	10.42 10.64	270-276	301.37	53.5
4c	$C_{17}H_{17}NO_4S$	61.55 61.61	5.15 5.17	4.20 4.23	9.75 9.68	318-22	331.39	49.5
4d	$C_{16}H_{15}NO_2S$	67.27 67.34	5.14 5.30	4.87 4.91	11.50 11.24	288-297	285.36	75.6
12	$C_{18}H_{21}NO_5S$	59.15 59.49	5.64 5.82	3.70 3.85	8.97 8.82	167-172	363.43	84.6

* For a crude sample.

TABLE 2. IR and UV Spectra of Compounds **4a-d** and **12**

Compound	IR spectrum, ν, cm^{-1}	UV spectrum, λ, nm (log ε)	
		λ_{max}	λ_{min}
4a	3100-2830, 1685 sh., 1672, 1608, 1580, 1565-1540, 1473-1445, 1396, 1347, 1320, 1285, 1230, 876, 830, 769	202.4 (4.56), 230.0 (4.08), 265.0 (4.13), 302.4 (4.09)	219.1 (4.01), 245.9 (3.81), 280.0 (3.95)
4b	3050-2830, 1700-1665, 1625, 1580, 1560, 1500, 1464, 1422, 1368, 1350, 1320, 1284, 1272, 1064, 1035, 880, 866, 827	227.7 (4.06), 265.0 (4.13), 303.8 (4.09)	213.3 (3.91), 242.4 (3.69), 281.5 (3.89)
4c	3100-2830, 1705-1670, 1610, 1594, 1565, 1513, 1459, 1445 sh., 1399, 1335, 1325 sh., 1260, 1220, 1142, 1110, 1022, 960, 872, 830, 820 sh.	201.5 (4.55), 228.8 (4.05), 265.0 (4.16), 303.8 (4.09)	218.8 (4.01), 245.0 (3.79), 279.7 (3.98)
4d	3000-2830, 1698 br., 1630, 1596, 1573, 1560 sh., 1500, 1477, 1460 sh., 1405, 1380, 1360-1330, 1307, 1292, 1240, 897, 811, 797, 770, 755	264.6 (4.20), 303.9 (4.11)	238.1 (3.80), 281.2 (3.86)
12	3120-2500, 1670, 1615, 1575, 1460, 1420, 1395, 1350, 1305, 1280, 1222, 1172, 1078, 1020, 971, 821	226.5 (4.26), 250.0 (4.19), 271.2 (4.26), 305.4 (3.90), 352.7 (3.62)	207.3 (4.14), 240.0 (4.12), 255.2 (4.17), 292.3 (3.89), 331.6 (3.53)

The most intense AB must be assigned to the electronic transition of the chromophores of the aromatic rings **A**. Unlike the UV spectra of 8-aza-, 8-aza-16-oxa-, and 8,16-diazasteroids [21], an additional AB was present at 227-230 nm in the spectra of compounds **4a-c**, in addition to the AB at 265 and 298-303 nm, which must probably be assigned to the electronic transitions of the C(17)-thiolactone chromophore. An important feature of the electronic absorption spectra of compounds **4a-c** is the broadened character of all the observed AB with half-width varying from 30 to 50 nm. Differentiation of the spectral contours showed that the most long wave bands (298-303 nm) have a complex composite character and are caused by the presence of two AB, located at ~292 and 303-310 nm. The AB at 227-230 and ~265 nm were not resolved on differentiation which indicates their noncomposite character, and their width is probably caused by a significant contribution of vibrational states. The rather stable character of the optical densities of the separate AB ($\Delta \log \varepsilon$ 0.01-0.03) should also be mentioned.

The UV spectra of compounds **4a-c** are rather characteristic and may serve as an important criterion for qualitative and quantitative assignments in this series.

Intense broadened and asymmetric AB are present at 1670-1695 cm^{-1} in the IR spectra of these compounds (Table 2), which on differentiation are splitted at least to two intense AB. These bands may possibly be explained by resonance effects (Fermi resonance), by the effects of the field of the C(12),C(17)-β-dicarbonyl fragment, or by some of the concepts of "mesomeric tautomerism" [22-24]. The AB at 1400-1630 cm^{-1} are probably caused by vibrations of the C=C bond, the bands at 700-900 cm^{-1} by the C–N bending vibrations of the tertiary nitrogen atom, and the bands at 1200-1350 cm^{-1} by the thiolactone fragment vibrations [22,23].

The ^{1}H NMR spectra are the most characteristic of thiagonanes **4a-c** and contain a number of resonance signals in the expected regions of the spectrum consistent with their structure. In the ^{1}H NMR spectra of derivatives **4a-c** there are resonance signals of the axial protons at C(9) displayed at 5.35-5.45 ppm as two doublets, due to spin–spin interactions with the vicinal protons of the methylene group at C(11). This group of protons is an ABX spin system, the X part of which is the proton at C(9). In the case of compound **4d** with a C(11) methyl substituent the resonance signal of the C(9) proton is located at 5.10 ppm and is displayed as a weakly resolved doublet with vicinal constant J = 1.5 Hz with the proton at C(11). This indicates the *trans* configuration of the C(9) and C(11) centers and as a result the shielded character of the C(9) and C(11) protons [25].

The presence at 4.75-4.82 ppm of a strongly coupled AB spin system for the protons of the methylene group at C(15) ($\Delta\delta \sim 14$ Hz, $J \sim 17.0$-17.5 Hz) is rather characteristic for this series of compounds. Also specific both in position and in shape are the resonance signals for the protons of the C(7) methylene group linked to the electronegative nitrogen atom, which are displayed as two triplets at 3.75-3.90 ppm, and a doublet, a multiplet, and a doublet at 4.28-4.34 ppm. From an analysis of the spin–spin interactions observed and in accordance with the Karplus principle [25] the low field signals (4.16-4.34 ppm) were assigned to C(7)-H_{eq} and the high field signals (3.50-3.89 ppm) to C(7)-H_{ax}.

The resonance signals of the protons of the methylene groups at C(11) and C(6) overlap one another at 2.93-3.56 ppm and may be displayed separately only on using double resonance procedures or the nuclear Overhauser effect [26]. The signals of the aromatic ring **A** protons and the methoxy substituents were observed in the usual spectral regions for such groups [19,20].

The ^{1}H NMR data of derivatives **4a-c** and comparison of them with the corresponding characteristics of 8-aza- [19], 8-aza-16-oxa- [5], and 8,16-diazasteroids [8] confirm our correctness of the assignments. We note that the ^{1}H NMR spectra of compounds **4a-c** were registered in trifluoroacetic acid solution, due to their exceptionally low solubility in other solvents available for NMR investigations. Such a low solubility for these compounds is probably the result of the high polarizability of the N^8–C^{14}=C^{13}(–C^{12}=O)–C^{17}=O fragment. This causes the high dipole moment for these derivatives, reaching 8-9 D according to quantum-chemical calculations, and leads to an extremely strong intermolecular interactions in the crystalline state. This circumstance prevents the chemical modification of these compounds. Attempts to obtain oximes at the C(12)

TABLE 3. ^{1}H and ^{13}C NMR Spectra of the Synthesized Compounds **4a-d**, **12**, and **14**

Compound	^{1}H NMR, δ, ppm, *J* (Hz)	^{13}C NMR, δ, ppm
4a	1.62-1.82 (2H, m, $C_{(11)}H_2$); 2.32-2.46 (2H, m, $C_{(12)}H_2$); 2.84 (1H, tt, *J* = 15.0; 3.0; 3.0; $C_{(6)}H_e$); 3.04 (1H, dtd, *J* = 15.0; 12.5; 5.0; $C_{(6)}H_a$); 3.39 (1H, ddd, *J* = 12.5; 12.5; 3.0; $C_{(7)}H_a$); 3.86 (1H, qq, *J* = 12.5; 5.0; 3.0; $C_{(7)}H_e$); 3.96 (2H, s, $C_{(15)}H_2$); 4.55 (1H, d.d, *J* = 10.0, 1.5, $C_{(9)}H_a$); 7.10-7.32 (4H, m, $C_{(1)}H$, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$)	20.18 ($C_{(11)}$); 29.66 ($C_{(12)}$); 29.79 ($C_{(6)}$); 31.88 ($C_{(15)}$); 43.62 ($C_{(7)}$); 57.21 ($C_{(9)}$); 106.76 ($C_{(13)}$); 126.12; 126.80; 126.89; 128.78; 133.86; 135.81; 164.08 ($C_{(14)}$); 192.51 ($C_{(17)}$)
4b	1.53-1.84 (2H, m, $C_{(11)}H_2$); 2.30-2.44 (2H, m, $C_{(12)}H_2$); 2.80 (1H, tt, *J* = 15.5; 3.0; 3.0; $C_{(6)}H_e$); 3.00 (1H, dtd, *J* = 15.5; 12.0; 4.0; $C_{(6)}H_a$); 3.38 (1H, ddd, *J* = 12.0; 12.0; 3.0; $C_{(7)}H_a$); 3.82 (3H, s, OCH_3), 3.85 (1H, qq, *J* = 12.0; 4.0; 3.0; $C_{(7)}H_e$); 3.96 (2H, s, $C_{(15)}H_2$); 4.50 (1H, dd, *J* = 10.0; 2.0; $C_{(9)}H_a$); 6.68 (1H, d, *J* = 2.5, $C_{(4)}H$); 6.84 (1H, dd, *J* = 8.5; 2.5; $C_{(2)}H$); 7.18 (1H, d, *J* = 8.5, $C_{(1)}H$)	20.69 ($C_{(11)}$); 30.37 ($C_{(12)}$); 30.51 ($C_{(6)}$); 32.50 ($C_{(15)}$); 44.27 ($C_{(7)}$); 55.92 (OCH_3); 57.47 ($C_{(9)}$); 107.47 ($C_{(13)}$); 113.71; 113.99; 127.83; 128.60; 135.80; 158.84($C_{(3)}$); 164.69 ($C_{(14)}$); 193.13 ($C_{(17)}$)
4c	1.58-1.84 (2H, m, $C_{(11)}H_2$); 2.31-2.43 (2H, m, $C_{(12)}H_2$); 2.73 (1H, tt, *J* = 15.0; 3.0; 3.0; $C_{(6)}H_e$); 2.97 (1H, dtd, *J* = 15.0; 12.0; 5.0; $C_{(6)}H_a$); 3.34 (1H, ddd, *J* = 12.0; 12.0; 3.0; $C_{(7)}H_a$); 3.86 (1H, qq, *J* = 15.0; 5.0; 3.0; $C_{(7)}H_e$); 3.88 (6H, s, $2OCH_3$); 3.95 (2H, s, $C_{(15)}H_2$); 4.48 (1H, dd, *J* = 10.5; 1.5; $C_{(9)}H_a$); 6.63 (1H, s, $C_{(4)}H$); 6.72 (1H, s, $C_{(1)}H$) [1.88 (1H, dddd, *J* = 12.0; 11.0; 11.0; 5.0; $C_{(11)}H_a$); 2.50-2.83 (2H, m, $C_{(11)}H_e$, $C_{(12)}H_a$); 2.94 (1H, tt, *J* = 12.0; 5.0; 5.0; $C_{(12)}H_e$); 3.00 (1H, tt, *J* = 14.0; 4.0; 4.0; $C_{(6)}H_e$); 3.14 (1H, ddd, *J* = 12.0, 4.0; 4.0; $C_{(6)}H_a$); 3.77 (1H, ddd, *J* = 12.0; 12.0; 4.0; $C_{(7)}H_a$); 4.00 (6H, s, $2OCH_3$); 4.12 (1H, tt, *J* = 12.0; 12.0; 4.0; $C_{(7)}H_e$); 4.54 (2H, s, $C_{(15)}H_2$); 4.86 (1H, dd, *J* = 11.0; 3.0; $C_{(9)}H_a$); 6.90 (1H, s, $C_{(4)}H$); 6.96 (1H, s, $C_{(1)}H$)]*	20.23 ($C_{(11)}$); 29.23 ($C_{(12)}$); 30.17 ($C_{(6)}$); 31.90 ($C_{(15)}$); 43.78 ($C_{(7)}$); 55.97 (OCH_3); 56.12 (OCH_3); 57.08 ($C_{(9)}$); 106.85 ($C_{(13)}$); 109.13($C_{(4)}$); 111.41($C_{(1)}$) ; 125.99 ($C_{(10)}$); 127.65 ($C_{(5)}$); 147.94 ($C_{(2)}$); 148.12 ($C_{(3)}$); 164.12 ($C_{(14)}$); 192.58 ($C_{(17)}$) 20.78 ($C_{(11)}$); 29.78 ($C_{(12)}$); 30.49 ($C_{(6)}$); 37.50 ($C_{(15)}$); 49.07 ($C_{(7)}$); 57.42 (OCH_3); 57.75 (OCH_3); 60.87 ($C_{(9)}$); 110.79 ($C_{(13)}$); 112.01 ($C_{(4)}$); 114.04 ($C_{(1)}$) ; 128.38 ($C_{(10)}$); 129.10 ($C_{(5)}$); 149.82 ($C_{(2)}$); 150.05 ($C_{(3)}$); 175.92 ($C_{(14)}$); 192.47 ($C_{(17)}$)
4d	0.78 (3H, d, *J* = 7.0, $C_{(11)}CH_3$); 2.74 (1H, m, $C_{(11)}H$); 2.99 (1H, tt, *J* = 12.0; 4.0; 4.0; $C_{(6)}H_e$); 3.12 (1H, ddd, *J* = 12.0; 12.0; 4.0; $C_{(6)}H_a$); 3.50 (1H, ddd, *J* = 12.0; 12.0; 4.0; $C_{(7)}H_a$); 4.04 (1H, d, *J* = 18, $C_{(15)}H_B$); 4.16 (1H, tt, *J* = 12.0; 4.0; 4.0; $C_{(7)}H_e$); 4.24 (1H, d, *J* = 18.0, $C_{(15)}H_A$); 5.10 (1H, d, *J* = 1.5, $C_{(9)}H$); 7.15 (1H, dd, *J* = 8.0; 2.0; $C_{(1)}H$); 7.21-7.42 (3H, m, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$)	10.71 ($C_{(11)}CH_3$); 30.11 ($C_{(6)}$); 35.17 ($C_{(15)}$); 45.23 ($C_{(11)}$); 48.73 ($C_{(7)}$); 64.84 ($C_{(9)}$); 108.83 ($C_{(13)}$); 127.42 (CH); 129.84 ($C_{(10)}$); 130.49 (CH); 130.83 (CH); 130.93 (CH); 135.46 ($C_{(5)}$); 177.36 ($C_{(14)}$); 195.45 ($C_{(17)}$); 200.59 ($C_{(12)}$)
12	2.45 (3H, s, $C_{(7')}H_3$); 2.76 (3H, s, $C_{(9)}H_3$); 3.09 (2H, t, *J* = 8.0, $C_{(4)}H_2$); 3.61 (2H, s, $C_{(5')}H_2$); 3.96 (2H, t, *J* = 8.0, $C_{(3)}H_2$); 3.96 (3H, s, OCH_3); 4.02 (3H, s, OCH_3); 6.84 (1H, s, $C_{(8)}H$); 7.15 (1H, s, $C_{(5)}H$); 7.6-9.3 (1H, br. s, N^+H)	19.88 ($C_{(7')}$); 25.32 ($C_{(4)}$); 29.20 ($C_{(9)}$); 37.53 ($C_{(5')}$); 41.71 ($C_{(3)}$); 6.47 (OCH_3); 56.55 (OCH_3); 109.03 ($C_{(3')}$); 110.82 (CH); 111.06 (CH); 118.39 ($C_{(8a)}$); 132.77 ($C_{(4a)}$); 148.77 ($C_{(6)}$); 156.01 ($C_{(7)}$); 172.41 ($C_{(1)}$); 194.09 ($C_{(6')}$); 196.31 ($C_{(2')}$); 197.31 ($C_{(4')}$)
14	3.08 (2H, t, *J* = 7.8, $C_{(4)}H_2$); 3.94 (2H, t, *J* = 7.8, $C_{(3)}H_2$); 3.94 (3H, s, OCH_3); 4.02 (3H, s, OCH_3); 6.84 (1H, s, $C_{(8)}H$); 7.15 (1H, s, $C_{(5)}H$)	25.29 ($C_{(4)}$); 41.53 ($C_{(3)}$); 56.45 (OCH_3); 56.54 (OCH_3); 109.15 ($C_{(3')}$); 110.83 (CH); 111.11 (CH); 118.27 ($C_{(8a)}$); 132.82 ($C_{(4a)}$); 148.77 ($C_{(6)}$); 156.10 ($C_{(7)}$); 172.49 ($C_{(1)}$); 194.23 ($C_{(6')}$); 195.94 ($C_{(2')}$); 196.25 ($C_{(4')}$)

* Spectra were recorded in CF_3COOD.

carbonyl group of thiagonanes **4a-c,** by analogy with the previously described derivatives of 8-aza-16-oxasteroids [7], proved to be unsuccessful. Also unsuccessful was the desulfurization of derivatives **4a-c** over Raney nickel to obtain a 3,4-disubstituted benzo[*a*]quinolizine.

The results of an investigation of the annelation reaction ([2+4]-cyclocondensation) of compounds **2a-c** and **11** with acids **3a,b** together with data of previous investigations [15,16,18-20] make it possible to confirm that the reaction is proceeded through the six-membered transition state **24** with the simultaneous formation of C–C and C–N bonds forming the partially hydrogenated pyridine ring **C**. Carrying out the cyclocondensation in alcohols stops the reaction at the stage of forming an equilibrium mixture of adducts of C-C addition **6** and **7** mutually converting through the ionic complex **5**. The introduction of a methyl substituent at position C(1) of compound **2** prevents the formation of the geometry of the six-membered transition state required for cyclocondensation, makes it sterically impossible to form C,C-addition adducts of type **6** and **7** and stops the reaction at the stage of forming salt **12**. The results of the H/D isotopic exchange of salt **12** indicate that together with the known tautomeric equilibrium of acid **3a** [13], a tautomeric equilibrium exists for its anions, involving also the protons of the acetyl and methylene group of the thiolactone cycle in the sphere of isotopic exchange. These data essentially explain the nucleophilicity of the acetyl methyl group and the 1,4-dipolarophilic properties of acids **3a,b** in the reaction with cyclic azomethines **2a-c**.

EXPERIMENTAL

3,4-Dihydroisoquinolines **2a-c** and **11** were obtained by the Bischler–Napieralski reaction [27], and 3-acylthiotetronic acids **3a,b** were synthesized by the method of [28,29]. A check on the progress of reactions and the homogeneity of products **4a-c** was effected by TLC (Silufol UV-254, chloroform–methanol, 8:2). Melting points were determined on a Boetius hot stage. The IR spectra were taken on a UR 20 instrument in KBr tablets. The UV spectra were recorded on a Specord M 400 spectrophotometer in ethanol. Mass spectra were recorded on a Varian MAT 311 spectrometer at an energy of the ionizing radiation of 70 eV. The ^{1}H and ^{13}C NMR spectra were run on a Bruker AC 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) spectrometer in trifluoroacetic acid (internal standard TMS). The modes and conditions of recording the spectra corresponded to those given in [30]. The ^{13}C and ^{13}C-{^{1}H} spectra were recorded using PGD and GD programms included in the mathematical provision of the instrument.

8-Aza-16-thiagona-1,3,5(10),13-tetraene-12,17-dione (4a). A mixture of isoquinoline **2a** (1.86 g, 14.2 mmol) and 3-acetylthiotetronic acid **3a** (2.24 g, 14.2 mmol) in glacial acetic acid (50 ml) was refluxed for 9 h, and then left overnight at room temperature. The separated substance was removed, washed with a mixture of acetic acid and ether (1:1), and dried. Substance **4a** (3.00 g) was obtained as orange crystals, and was recrystallized from a mixture of acetic and trifluoroacetic acids (2:1).

8-Aza-3-methoxy-16-thiagona-1,3,5(10),13-tetraene-12,17-dione (4b). A solution of acid **3a** (0.98 g, 6.2 mmol) in glacial acetic acid (25 ml) was added to a solution of 6-methoxy-3,4-dihydroisoquinoline **2b** (1.0 g, 6.2 mmol) in glacial acetic acid (25 ml), and the mixture obtained was refluxed for 12 h in an atmosphere of argon. The separated substance (0.6 g) was removed, and washed with acetic acid. The filtrates were combined, and refluxing was continued for a further 7 h. Once again the precipitated crystals (0.3 g) were removed, washed with acetic acid, the filtrated were combined, evaporated to 25-30 ml, and refluxing continued for a further 8 h. The precipitated substance (0.2 g) was removed, washed with acetic acid, combined with the previously obtained portions, and recrystallized from a mixture of trifluoroacetic and acetic acids (1:1). Compound **4b** (1 g) was obtained as brown crystals.

8-Aza-2,3-dimethoxy-16-thiagona-1,3,5(10),13-tetraene-12,17-dione (4c). A mixture of 6,7-dimethoxy-3,4-dihydroisoquinoline **2c** (1.0 g, 5.2 mmol) and acid **3a** (0.83 g, 5.3 mmol) in glacial acetic acid (60 ml) was refluxed for 17 h in an atmosphere of argon. The precipitated crystals were removed, washed

with glacial acetic acid, and recrystallized from a mixture of trifluoroacetic and acetic acids (1:1). Compound **4c** (0.89 g) was obtained as yellow crystals.

8-Aza-11-methyl-16-thiagona-1,3,5(10),13-tetraene-12,17-dione (4d). A mixture of 3,4-dihydroisoquinoline **2a** (1.86 g, 4.2 mmol) and acid **3b** (2.0 g, 4.2 mmol) in acetic acid (50 ml) was refluxed for 9 h then left overnight at room temperature. The separated crystals were filtered off, washed with a mixture of acetic acid and ether (1:1), dried, and recrystallized from a mixture of acetic and trifluoroacetic acids (2:1). Compound **4d** (3.01 g) was obtained as light brown prismatic crystals.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinolinium 3-Acetylthiotetronate (12). A solution of acid **3a** (0.24 g, 1.5 mmol) in ethanol (20 ml) was added to a solution of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **11** (0.31 g, 1.5 mmol) in ethanol (10 ml). The mixture obtained was left overnight at 15°C, then evaporated to half volume, diluted with an equal volume of ether, and left for 1 day at 15°C. The precipitated light brown crystals were filtered off, washed with cold ethanol, and with ether, dried, and salt **12** (0.12 g) was obtained. The mother liquor was diluted with an equal volume of ether, and left for 1 day at 0°C. The precipitated solid was filtered off, washed with ether, dried, and further salt **12** (0.34 g) was obtained. The total yield was 0.46 g.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinolinium [2,5',5',7',7',7',9,9,9-(9)-^{2}H]-3-Acetylthiotetronate (14) was obtained in a sample tube for NMR investigations from salt **12** (0.05 g, 0.14 mmol) and D_2O (3 × 0.25ml, 12.5 mmol, D content 99.8%) in $CDCl_3$ (0.4 ml). The degree of isotopic exchange was >95%.

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REFERENCES

1. M. V. Budnikova, L. G. Lis, and A. L. Mikhal'chuk, *Zh. Obshch. Khim.,* **69**, 1053 (1999).
2. M. V. Budnikova, D. B. Rubinov, L. G. Lis, A. L. Mikhal'chuk, *Mendeleev Commun.*, 208 (1999).
3. A. A. Akhrem, B. B. Kuz'mitskii, F. A. Lakhvich, V. A. Khripach, Yu. L. Zhuravkov, *Chemistry and Biology of Immunoregulators* [in Russian], Zinatne, Riga (1985), p. 265.
4. N. A. Konoplya, O. V. Gulyakevich, A. L. Mikhal'chuk, and B. B. Kuz'mitskii, *Ves. Akad. Nauk BSSR, Ser. Khim. Navuk*, No. 3, 91 (1994).
5. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and V. N. Pshenichnyi, *Zh. Org. Khim.*, **15**, 1396 (1979).
6. A. A. Akhrem. F. A. Lakhvich, V. N. Pshenichnyi, and O. F. Lakhvich, *Dokl. Akad. Nauk SSSR*, **240**, 595 (1978).
7. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and V. N. Pshenichnyi, *Dokl. Akad. Nauk BSSR*, **22**, 431 (1978).
8. V. N. Pshenichnyi, F. A. Lakhvich, and V. A. Khripach, *Ves. Akad. Nauk BSSR, Ser. Khim. Navuk*, No. 5, 70 (1991).
9. M. von Strandtmann, M. P. Cohen, and J. Shavel, *J. Org. Chem.*, **31**, 797 (1966).
10. A. A. Akhrem. A. M. Moiseenkov, V. A. Krivoruchko, F. A. Lakhvich, and A. I. Poselenov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2078 (1972).
11. J. C. Pelletier and M. P. Cava, *Synthesis*, 474 (1987).
12. G. Becker, *Introduction to the Electronic Theory of Organic Reactions*, [Russian translation], Mir, Moscow (1977).
13. T. Yamaguchi, K. Saito, T. Tsujimoto, and H. Yuki, *J. Heterocycl. Chem.*, **13**, 533 (1976).
14. K. Saito and T. Yamaguchi, *J. Chem. Soc., Perkin Trans. 2*, 1605 (1979).

15. A. L. Mikhal'chuk, O. V. Gulyakevich, Yu. V. Shklyaev, V. S. Shklyaev and A. A. Akhrem, *Zh. Obshch. Khim.*, **67**, 2062 (1997).
16. A. L. Mikhal'chuk, O. V. Gulyakevich, Yu. V. Shklyaev, V. S. Shklyaev, and A. A. Akhrem, *Khim. Geterotsikl. Soedin.*, 681 (1998).
17. E. Yu. Gudriniece (editor), *Structure and Tautomeric Conversions of β-Dicarbonyl Compounds* [in Russian], Zinatne, Riga (1977).
18. S. Bolvig, F. Dnus, and P. E. Hansen, *Magn. Reson. Chem.*, **36**, 315 (1998).
19. A. L. Mikhal'chuk, O. V. Gulyakevich, A. A. Zenyuk, A. V. Korchik, L. G. Lis, V. A. Kripach, L. I. Ukhova, and A. A. Akhrem, *Dokl. Akad. Nauk*, **317**, 1397 (1991).
20. O. V. Gulyakevich, A. L. Mikhal'chuk, and A. A. Akhrem, *Khim. Geterotsikl. Soedin.*, 1239 (1993).
21. V. Z. Kurbako, N. I. Garbuz, and L. G. Lis, *Zh. Prikl. Spectroscp.*, **38**, 407 (1983).
22. L. J. Bellamy, *New Data on the Infra-Red Spectra of Complex Molecules* [Russian translation], Mir, Moscow (1971).
23. A. D. Cross, *Introduction to Practical Infra-Red Spectroscopy* [Russian translation], Inostr. Lit., Moscow (1961)
24. A. L. Mikhal'chuk, A. I. Verenich, O. V. Gulyakevich, and A. A. Akhrem, *Dokl. Russ. Akad. Nauk*, **356**, 769 (1997).
25. M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
26. R. Bible, *Interpretation of Nuclear Magnetic Resonance Spectra* [Russian translation], Atomizdat, Moscow (1969), p. 224.
27. W. M. Whalley and T. R. Govindachary, *Organic Reactions* [Russian translation], Inostr. Lit., Moscow (1953), No. 6, p. 98.
28. E. Benary, *Ber.*, **43**, 1943 (1910).
29. E. Benary, *Ber.*, **46**, 2103 (1913)
30. V. N. Pshenichnyi, O. V. Gulyakevich, E. V. Borisov, and V. A. Khripach, *Zh. Org. Khim.,* **23**, 1765 (1987).