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SYNTHESIS AND PROPERTIES OF 12(*E*)-ETHOXYIMINO DERIVATIVES OF 8-AZA-16-THIAGONA-12,17-DIONES

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The reaction of 8-aza-16-thiagona-1,3,5(10),13-tetraene-12,17-dienes with ethoxyimine in dimethyl sulfoxide yields the corresponding 12(E)-ethoxyimino derivatives. The physicochemical properties of these compounds were studied.

Keywords: 8-aza-16-thiagona-12,17-diones, heterosteroids, 12(*E*)-ethoxyimino-8-aza-16-thiagona-17-ones, 12(*E*)-ethoxyimino-1H-thieno[3',4':5,6]pyrido[2,1-*a*]isoquinolin-1-ones.

8-Azasteroids, their *D*-homoanalogs, and heteroanalogs with oxygen, nitrogen, sulfur atoms at the 16(17) position of the tetracyclic 8-azasteroid skeleton display biological properties [1-4] and, thus, have been studied in the search for new pharmacological agents for the regulation of biological function and control of the biochemical homeostasis of man and farm animals. 8-Aza-16-thiagona-12,17-diones [5, 6] have received special attention due to the biophoric properties related to their nitrogen and sulfur atoms [7, 8]. However, the extremely low solubility of these azathiasteroids severely limits their possible modification and biological screening. Thus, these compounds must be transformed to increase their solubility while retaining their basic structural elements. The replacement of the 12-carbonyl group in 1-azagona-12,17-*D*-homodiones by imino or hydroxyimino functions, on the whole, does not alter the biological activity of these compounds and, in some cases, even enhances it. On the other hand, such derivatives, as a rule, are more soluble than their dioxo precursors. Hence, we attempted to obtain imino or hydroxyimino derivatives of 8-aza-16-thiagona-12,17-diones to study their chemical and biological properties.

The first attempts to obtain hydroxyimino derivatives of 8-aza-16-thiagona-12,17-diones under the conditions used for transforming 8-aza-16-oxagona-12,17-diones [9], proved unsuccessful [6, 10]. In further work, we found that 8-aza-16-thiagona-12,17-diones **1a**,**b** are quite soluble in DMSO at 80-100°C and remain chemically stable under these conditions over a long period. This finding was used in the synthesis of ethoxyimino derivatives **2a**,**b**.

The condensations of 8-aza-16-thiagona-12,17-diones **1a**,**b** with ethoxyamine were carried out in solutions of these reagents in DMSO at 80-100°C with monitoring by thin-layer chromatography. At the end of the reaction upon the complete consumption of substrates **1a**,**b**, the reaction mixtures were diluted with water and the precipitates filtered off. Usual work-up of the crude products gave analytical samples of 12(*E*)-ethoxyimino derivatives **2a**,**b**.

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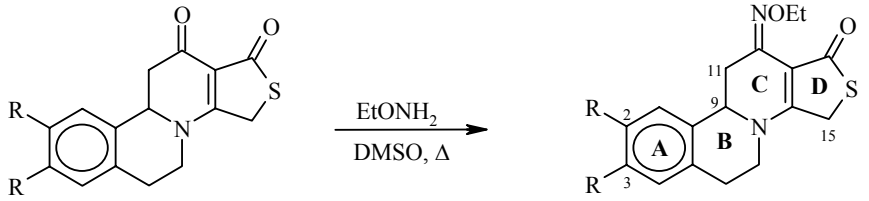

1a,**b** **2a**,**b**

a R = H, **b** R = OMe

Under these conditions for the reaction of substrates **1a**,**b** with ethoxyamine, we might have expected the formation of pyrido[2,1-*a*]isoquinoline derivatives **3** or 17-ethoxyimino derivatives **4** in addition to desired products **2a**,**b**. These additional products could be formed as the result of attack of nucleophilic ethoxyamine at the electrophilic thiolactone group $C_{(17)}$=O. On the other hand, the formation of 12-ethoxyimino derivatives **2a**,**b** as mixtures of *E-(anti)-* and *Z-(syn)*-stereoisomers is very likely. However, the thin-layer chromatographic monitoring of the reaction course and spectral investigation of **2a**,**b** indicated that there were no other products of the reaction of substrates **1a**,**b** with ethoxyamine.

3 **4**

The composition and structure of products **2a,b** are in accord with the elemental analysis data and physicochemical data. The IR spectra of 12-ethoxyimino derivatives **2a,b**, on the whole, support their proposed structure. A number of specific features are found, which would be difficult to explain without additional spectral investigation. Thus, in the 1700-1600 cm^{-1} region, the spectrum of **2a** shows strong bands (85%) at 1680 and 1610 cm^{-1} and a medium-strength band (55%) at 1650 cm^{-1}, while, in this region, **2b** has only one strong band (85%) at 1652 cm^{-1} but two medium-strength bands (60-70%) at 1695 and 1620 cm^{-1}.

All these bands are broadened and asymmetrical, indicating the presence of various components. While the high-frequency bands at 1695 and 1685 cm^{-1} may be reliably assigned to C=O group vibrations, it is difficult to assign the bands at lower frequencies to C=N or C=C bonds. We should note that one strong broadened and symmetrical band is found for **2b** at 1500-1400 cm^{-1} at ~1470 cm^{-1}, while two medium-strength bands are found in this region for **2a** at 1488 and 1460 cm^{-1} due to vibration of the C=C bonds of the aromatic ring **A** [10].

The electronic absorption spectra of **2a,b**, as in the case of starting **1a,b** [5, 6], show strong bands at ~320 and ~280 nm, which, in general, indicates that there are only slight differences in the electronic structures of these compounds. On the other hand, a very broad, low-intensity band with maximum at ~410 nm is noted in the UV spectrum of **2b**, which may be assigned to $n \rightarrow \pi^*$ electronic transitions [11].

The ^{1}H NMR spectra of ethoxyimino derivatives **2a,b** show signals for all the protons of their proposed structures. Thus, in the 4.50-4.70 ppm region, the signal for 9-H appears as the X-part of the $C_{(9)}HC_{(11)}H_2$ ABX-spin system. The signals for $C_{(15)}H_2$ appear at 3.95-4.06 ppm as a strongly coupled AB-spin system [12]. In contrast to the ^{1}H NMR spectra of starting **1a,b** [5, 6], the spectra of derivatives **2a,b** have characteristic ethyl group signals as a three-proton triplet (at ~1.30 ppm) and two-proton quartet (at ~4.18 ppm). Two three-proton singlets are found for **2b**, which has 2- and 3-OMe substituents in ring **A**, as well as singlets for 1-H and 4-H shifted upfield. We should note that no ^{1}H NMR signals were found corresponding to the *Z-(syn)*-configuration of the OEt group of the 12-ethoxyimino substituent. Support for the *E*-configuration of the ethoxy group is

found in the position of the signals of the ABX-system for the protons at $C_{(9)}$ and $C_{(11)}$. Thus, in contrast to **1a,b** [5, 6], the signals for the protons in **2a,b** are shifted upfield by about 160 and 180 Hz for $C_{(9)}H_X$ and $C_{(11)}H_A$, respectively, and by 80 Hz for $C_{(11)}H_B$. Such a displacement cannot be attributed only to the change in electronegativity upon replacing the oxygen atom by an ethoxyimino group but is quite clear taking account of the anisotropic effect of an ethoxy substituent with *E*-configuration.

The ^{13}C NMR spectra of derivatives **2a,b** show the corresponding number and type of ^{13}C signals for the assigned structures. In particular, the ethoxyimino substituent methyl groups are found in the region up to 20 ppm, while the signals for the $^{13}C_{(17)}$-thiolactone carbonyl groups are found at 190-200 ppm. The signals for the ^{13}C-azomethine fragment are found at ~167 ppm, while the ^{13}C atoms of the $C_{(13)}=C_{(14)}$ vinyl fragment are found at ~104 and ~148 ppm, respectively. The ^{13}C NMR spectra also support the assigned *E*-configuration of the ethoxyimino group in **2a,b**: the signals for $^{13}C_{(9)}$ and $^{13}C_{(11)}$ are shifted upfield by ~4 and ~10 ppm, respectively, relative to the corresponding signals in **1a,b** [5, 6].

We should note that products **2a,b** are much more soluble and have much lower melting points in comparison with their 12,17-dioxo precursors. Thus, **2a** melts at about 100°C lower than precursor **1a**, while **2b** melts at 70°C lower than **1b** [5, 6].

Thus, ethoxyimino derivatives of 8-aza-16-thiagona-12,17-diones **2a,b** appear to be more convenient for further chemical transformations and biological testing, while the reported method provides for the preparation of other hydroxyimino and alkoxyimino derivatives of 8-aza-16-thiagona-12,17-diones **1**. We should note that the formation of ethoxyimino derivatives **2a,b** exclusively as *E*-isomers indicates the great significance of coulombic interactions in the stereochemistry of such imino compounds.

EXPERIMENTAL

Samples of 8-aza-16-thiagona-1,3,5(10),13-tetraene-12,17-diones **1a,b** were obtained by fusing the corresponding 3,4-dihydroisoquinolines using 3-acetylthiotetronic acid according to our previous procedures [5, 6]. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1 chloroform–methanol as the eluent. The melting points were determined on a Boetius block. The IR spectra were taken on a UR-20 spectrometer using KBr pellets. The UV spectra were taken on a Bruker AC-200 spectrometer for $CDCl_3$ solutions at 200 MHz for the ^1H NMR spectra and 50 MHz for the ^{13}C NMR spectra using TMS as the internal standard.

***rac*-12(*E*)-Ethoxyimino-8-aza-16-thiagona-1,3,5(10),13-tetraen-17-one (2a).** Ethoxyamine (0.11 ml, 1.5 mmol) was added to a solution of 8-aza-16-thiagona-12,17-dione **1a** (0.27 g, 1 mmol) in dimethylsulfoxide (30 ml) and the mixture obtained was maintained at 80°C for 24 h. Then, additional 0.07 ml (1 mol) of ethoxyamine was added, maintaining the mixture at the indicated temperature. Further samples of ethoxyamine (0.07 ml) were added after each additional 24 h period until the complete consumption of the starting azasteroid. The total reaction time was 80 h. The total amount of ethoxyamine used was 0.32 ml (4.5 mmol). At the end of the reaction, the desired product was precipitated from the reaction mixture by adding water, filtered off, and dissolved in chloroform. The solution obtained was dried over sodium sulfate and then evaporated to dryness. The residue was then recrystallized from ethyl acetate to give 0.26 g of ethoxyimino derivative **2a** in 82% yield as light-yellow crystals; mp 199-203°C (dec). IR spectrum, ν, cm^{-1}: 3080-2830, 1680, 1650, 1610, 1565, 1488, 1460, 1415, 1380, 1357, 1340, 1295, 1215, 1125, 1056, 1020, 943, 900, 875, 847, 772, 760, 685. UV spectrum, λ_{max}, nm (ε): 273.6 (13150), 316.8 (17900); λ_{min}, nm (ε): 233 (8040), 292.1 (9625). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, $J_{1,2}$ = 7.0, CH_3); 2.16 (1H, dd, J_1 = 13.0, J_2 = 16.0, 11-H_B); 2.81 (1H, tt, J_1 = 16.0, $J_{2,3}$ = 3.0, 6-He); 3.11 (1H, dtd, J_1 = 3.0, J_2 = 12.0, J_3 = 16.0, 6-H_a); 3.42 (1H, ddd, J_1 = 3.0, J_2 = 12.0, J_3 = 16.0, 7-H_a); 3.86 (1H, dd, J_1 = 3.0, J_2 = 16.0, 11-H_A); 3.95 (1H, tt, $J_{1,2}$ = 3.0, J_3 = 16.0, 7-H_e); 3.98 (1H, d, *J* = 17.0, 15-H_B); 4.10 (1H, d, *J* = 17.0, 15-H_A); 4.22 (2H, q, $J_{1,2,3}$ = 7.0, $NOCH_2$); 4.64 (1H, dd, J_1 = 3.0, J_2 = 13.0, 9-H_X);

7.17-7.42 (4H, m, 1-H, 2-H, 3-H, 4-H). ^{13}C NMR spectrum, δ, ppm: 15.323 (CH_3), 30.071 ($C_{(6)}$), 30.464 ($C_{(11)}$), 31.683 ($C_{(15)}$), 44.363 ($C_{(7)}$), 56.750 ($C_{(9)}$), 70.257 ($NO\underline{C}H_2$), 104.653 ($C_{(13)}$), 126.788 (CH), 127.843 (CH), 127.963 (CH), 129.434 (CH), 133.976 ($C_{(10)}$), 135.053 ($C_{(5)}$), 147.287 ($C_{(14)}$), 167.437 ($C_{(12)}$), 195.218 ($C_{(17)}$). Found, %: C 65.00, 64.79; H 5.89, 5.73; N 9.03, 8.84; S 10.02, 10.01. $C_{17}H_{18}N_2O_2S$. Calculated, %: C 64.95; H 5.77; N 8.91; S 10.20. M 314.40.

***rac*-12(*E*)-Ethoxyimino-2,3-dimethoxy-8-aza-16-thiagona-1,3,5(10),13-tetraen-17-one (2b).** The reaction of 8-aza-16-thiagona-12,17-dione **1b** (0.33 g, 1 mmol) with ethoxyamine according to a procedure analogous to the synthesis of **2a** gave 0.26 g (70%) of ethoxyimino derivative **2b** as light-yellow crystals; mp 245-250°C (dec.). IR spectrum, ν, cm^{-1}: 3100-2830, 1695, 1652, 1620, 1525, 1480-1455, 1398, 1358, 1320, 1282, 1234, 1225, 1140, 1062, 1050, 954, 936, 887, 861, 796. UV spectrum, λ_{max}, nm (ε): 210.5 (25730), 290 (23730), 317.3 (28760), 410 (1765); λ_{min}, nm (ε): 201.8 (25285), 253.2 (12745), 298.7 (20915), 368.2 (1400). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, $J_{1,2}$ = 7.5, CH_3); 2.17 (1H, dd, J_1 = 13.0, J_2 = 16.5, 11-H_B); 2.82 (1H, tt, $J_{1,2}$ = 3.0, J_3 = 15.5, 6-H_e); 3.06 (1H, dtd, J_1 = 4.0, J_2 = 15.5, J_3 = 17.0, 6-H_a); 3.39 (1H, ddd, J_1 = 4.0, $J_{2,3}$ = 17.0, 7-H_a); 3.78 (1H, dd, J_1 = 4.0, J_2 = 16.5, 11-H_A); 3.88 (3H, s, OCH_3); 3.92 (3H, s, CH_3); 3.96 (1H, tt, $J_{1,2}$ = 4.0, J_3 = 17.0, 7-H_e); 3.98 (1H, d, *J* = 17.5, 15-H_B); 4.06 (1H, d, *J* = 17.5, 15-H_A); 4.14 (2H, q, $J_{1,2,3}$ = 7.5, $NOCH_2$); 4.58 (1H, dd, J_1 = 4.0, J_2 = 13.0, 9-H_X); 6.66 (1H, s, 4-H); 6.74 (1H, s, 1-H). ^{13}C NMR spectrum, δ, ppm: 14.734 (CH_3), 29.363 ($C_{(6)}$), 30.002 ($C_{(11)}$), 31.269 ($C_{(15)}$), 43.902 ($C_{(7)}$), 55.991 ($C_{(9)}$), 55.991 (OCH_3), 56.298 (OCH_3), 69.587 ($NOCH_2$), 103.972 ($C_{(13)}$), 109.004 ($C_{(4)}$), 111.402 ($C_{(1)}$), 125.683 ($C_{(10)}$), 126.235 ($C_{(5)}$), 143.314 ($C_{(2)}$), 146.762 ($C_{(3)}$), 148.314 ($C_{(14)}$), 166.963 ($C_{(12)}$), 198.495 ($C_{(17)}$). Found, %: C 60.78, 60.75; H 6.03, 5.98; N 7.34, 7.41; S 8.51, 8.43. $C_{19}H_{22}N_2O_4S$. Calculated, %: C 60.94; H 5.92; N 7.48; S 8.56. M 374.46.

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REFERENCES

1. A. A. Akhrem, B. B. Kuz'mitskii, F. A. Lakhvich, V. A. Khripach, and Yu. L. Zhuravkov, *Chemistry and Biology of Immunoregulators* [in Russian], Zinatne, Riga (1985), p. 265.
2. N. A. Konoplya, O. V. Gulyakevich, A. L. Mikhal'chuk, and B. B. Kuz'mitskii, *Vestsi Akad. Navuk Belarusi, Ser. Khim. Navuk*, No. 3, 91 (1994).
3. G. S. Lyubin, I. G. Dad'kov, O. V. Gulyakevich, and B. B. Kuz'mitskii, *Vestsi Akad. Navuk Belorussk. SSR, Ser. Khim. Navuk*, No. 2, 93 (1990).
4. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and B. B. Kuz'mitskii, *Vestsi Akad. Navuk Belorussk. SSR, Ser. Khim. Navuk*, No. 6, 81 (1982).
5. M. V. Budnikova, L. G. Lis, D. B. Rubinov, and A. L. Mikhalchuk, *Mendeleev Commun.*, 208 (1999).
6. M. V. Budnikova, D. B. Rubinov, and A. L. Mikhal'chuk, *Khim. Geterotsikl. Soedin.*, 107 (2003).
7. N. K. Kochetkov (editor), *General Organic Chemistry (Nitrogen-containing Heterocycles)* [in Russian], Vol. 8, Khimiya, Moscow (1985), pp. 196, 255, 286.
8. E. R. Uzhdavini, *Toxicology of Organic Sulfur Compounds* [in Russian], Zinatne, Riga (1986), p.195.
9. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and V. N. Pshenichnyi, *Zh. Org. Khim.*, **15**, 1396 (1979).
10. A. Cross, *Introduction to Practical Infrared Spectroscopy* [Russian translation], Nauka, Moscow (1961), p. 111.
11. O. V. Sverdlova, *Electronic Spectra in Organic Chemistry* [in Russian], Khimiya, Leningrad (1973), p. 248.
12. R. Bible, *Interpretation of Nuclear Magnetic Resonance Spectra* [Russian translation], Atomizdat, Moscow (1969), p. 224.