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SHORT COMMUNICATIONS

Methylated Derivatives of 8-Aza-16-thia-D-homogona-1,3,5(10),13-tetraene-12,17-dione

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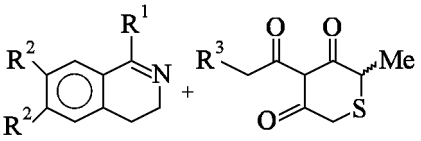
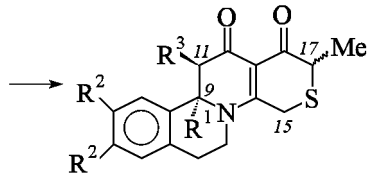
Heterocyclic analogs of steroids, in particular, azaanalogs [1–4] are used in medical practice [1, 3] and are subjected to physicochemical, medical, and biological investigations aimed at development of new pharmaceuticals [4]. We established formerly that annelation (cyclocondensation) of 3,4-dihydroquinolines with 4-acetylthiopyran-3,5-dione gave rise to a tetracyclic skeleton of thiopyrano[4',3':5,6]pyrido-[2,1-*a*]isoquinoline [5]. The compounds resulting from this reaction by their structural similarity belong to azathiaanalogs of steroids [2] and are of interest from theoretical and practical aspect in development of pharmacological agents of immunocontrol for medical, veterinary, and biotechnological applications. In view of above and taking into account the dependence of the direction and level of immunomodulating activity of 8-azasteroids on the presence of alkyl groups in definite positions of the heterosteroid skeleton [4, 6] the development of approaches to the synthesis of alkylated analogs of azathiasteroids was an important task.

For this purpose we studied annelation of 3,4-dihydroisoquinolines (**Ia, b**) with 4-acyltetrahydro-2*H*-thiopyran-3,4-diones (**IIa, b**) and found that these reactions yielded compounds **IIIa, b** with a tetracyclic 8-aza-15-thia-*D*-homogonane skeleton with methyl groups in pharmacologically important *9, 11, 17* positions. The structure of compounds **IIIa, b** was confirmed alongside the elemental analysis with the data of IR and UV spectroscopy evidencing the presence in their structure of N^{8}–C^{14}=C^{13}(C^{12}=O)–C^{17a}=O aminovinyldicarbonyl fragment [7]. Compound **IIIb** obtained is the first example of synthesis of diheteroatomic steroid derivatives with C^{9}-angular methyl group. It is significant that the reaction occurs regiospecifically providing only C^{17}-methyl derivatives, and the presumable C^{15}-methyl derivatives do not form. Relying on the observed coupling constant of vicinal protons attached to C^{9}, C^{11} we assigned to compound **IIIa** the *trans*-configuration of C^{11}-methyl group with respect to the benzyl proton at C^{9} atom. On the other hand, unlike the previously studied annelation of 3,4-dihydroisoquinolines with 2-acylcyclohexane-1,3-diones that proceeded regio- and stereospecifically [7] in the present case instead of the expected 17β-methyl derivatives mixtures of stereoisomeric at C^{17} (~45 : 55) 17ξ-methyl-8-aza-16-thia-D-homogona-12,17a-diones (**IIIa, b**) were obtained. This is indicated by the double set of signals in the ^{1}H NMR spectrum. In particular, from the C^{17}-methyl groups arise two doublets at δ 1.40–1.55 ppm (*J* 7.0 Hz).



Ia, b **IIa, b**



IIIa, b

R^1 = R^2 = H, R^3 = Me (a); R^1 = Me, R^2 = OMe, R^3 = H.

The described syntheses of methylated derivatives **IIIa, b** provide a simple and universal procedure for preparation of alkylated derivatives of 8-aza-D-homogonanes and the other 16-heteroatomic derivatives (oxa, aza) of 8-aza-D-homogonanes that are interest-

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ing objects for the study of structure–function relation in the series of immunotropic heterocyclic steroid analogs.

rac-11,17ξ-Dimethyl-8-aza-16-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIIa). A mixture of 0.2 g of 3,4-dihydroisoquinoline **Ia** and 0.13 g of β,β-triketone IIa in 5 ml of ethanol was boiled in an argon flow for 3 h. Then the reaction mixture was kept for 16 h at +5°C. The separated crystals were filtered off and recrystallized from ethanol. We obtained 0.22 g (77%) of 8-aza-16-thia-D-homogonane **IIIa** as yellow crystals, mp 202–204°C (decomp.). IR spectrum, cm^{-1}: 3050–2830, 1685, 1620, 1600, 1520, 1510, 1460, 1445, 1390, 1375, 1345, 1290, 1280, 1240, 1200, 1190, 1170, 1130, 1110, 1070, 1050, 1025, 990, 950, 910, 880, 860. UV spectrum, λ_{max}, nm (ε): 268.5 (9425), 314.7 (13096); λ_{min}, nm (ε): 238.6 (3300), 286.5 (5596). $[M]^+$ 313. Found, %: C 69.03, 68.89; H 6.02, 5.94; N 4.32, 4.39; S 10.39, 10.31. $C_{18}H_{19}O_2NS$. Calculated, %: C 69.98; H 6.11; N 4.47; S 10.23. *M* 313.42.

rac-11,17ξ-Dimethyl-2,3-dimethoxy-8-aza-16-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIIb) was prepared in a similar way from 0.21 g of 3,4-dihydroisoquinoline **Ib** and 0.19 g of triketone **IIb**. We obtained 0.17 g (47%) of 8-aza-16-thia-D-homogonane **IIIb** as yellow crystals, mp 178–180°C. IR spectrum, cm^{-1}: 3100–2830, 1695, 1630, 1530, 1520, 1480, 1460, 1450, 1360, 1340, 1310, 1270, 1230, 1205, 1150, 1075, 1050, 1015, 980, 960, 940, 910, 890. UV spectrum, λ_{max}, nm (ε): 201.45 (3427), 226.20 (8885), 274.10 (9060), 315.00 (9642); λ_{min}, nm (ε): 223.35 (8696), 247.05 (3992), 295.00 (6742). $[M]^+$ 373. Found, %: C 64.24, 64.19; H 6.28, 6.19; N 3.62, 3.60; S 8.76, 8.81. $C_{20}H_{23}O_4NS$. Calculated, %: C 64.32; H 6.21; N 3.75; S 8.59. *M* 373.47.

IR spectra were registered on spectrophotometer UR-20 from KBr pellets. UV spectra were measured on Specord M-400 instrument from alcoholic solutions. ^1H NMR spectra were registered on spectrometer Bruker AC-200 (200 MHz), internal reference TMS. Mass spectra were taken on mass spectrometer Shimadzu MS QP-5000 with direct sample admission, ionizing electrons energy 70 eV. The monitoring of reaction progress and checking of compounds homogeneity was done by TLC on Silufol UV-254 plates, eluent chloroform–methanol, 9:1, development under UV irradiation or by spraying iron(III) chloride solution. Melting points were determined on Boetius heating block.

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