

SHORT
COMMUNICATIONS

New N,S-Diheteroatomic Steroid Analogs. Annelation of 3,4-Dihydroisoquinolines by 3-Acetylthiopyran-2,4-dione

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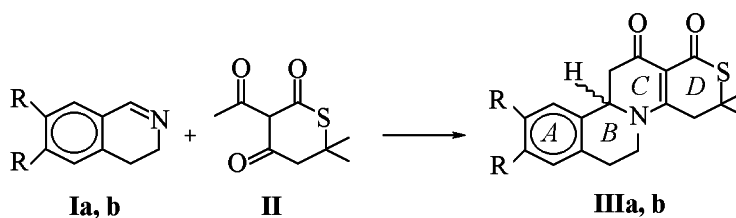
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Heterocyclic analogs of steroids, in particular, 8-aza- [1, 2], 8,16-diaza- [3], 8-aza-16-dioxa- [4], 8-aza-16-thia- [5], 8,17-diaza-*D*-homo- [1], and 8-aza-17-oxa-*D*-homoanalogs [6] are interesting both from theoretical and practical viewpoint as modulators of the immune response [7]. Therefore is quite understandable the attention drawn to the preparation and investigation of new steroid heteroanalogs with a target to establish the connection between the structure and its function and to elucidate the influence of the nature of heteroatom on the physico-chemical and biological characteristics of these compounds. The 8-aza-16 thiagonanes (thieno-[3,4:5,6]pyrido[2,1-*a*]isoquinolines) [5] described previously are hard to prepare that hampers their bioscreening and further chemical transformations. Therefore it seemed promising to obtain analogs of such compounds containing six-membered thiolactone cycle *D* and to test experimentally the previous

statement on the role of the size of the cyclic β -dicarbonyl fragment in the β,β -tricarbonyl compounds in the annealing of the cyclic Schiff's bases [8]. Aiming at solution of this problem we studied the reaction between 3,4-dihydroisoquinolines and 3-acetylthiopyran-2,4-dione. We thus obtained previously unknown 8-aza-17-thia-*D*-homogona-12,17a-diones (thiopyrano[3,4:5,6]pyrido[2,1-*a*]isoquinolines).

The investigation of the reaction between 3,4-dihydroisoquinolines **Ia, b** and 3-acetyl-6,6-dimethylthiopyran-2,4-dione (**II**) revealed that unlike reactions with five-membered heterocyclic β,β -tricarbonyl compounds (3-acetyltetronic [4], -thiotetronic [5], -tetramic acids [3]) the former processes occur cleanly at common boiling of the reagents mixture in alcohol resulting in the target 8-aza-17-thia-*D*-homogona-12,17a-diones (**IIIa, b**) that are *D*-homoanalogs of the previously reported 8-aza-16-thiagonanes [5].



R = H (a), OMe (b).

Thus prepared compounds are far better soluble than the previously studied thiazasteroids [5] that facilitates their bioscreening, physico-chemical investigations, and further structural and functional transformations.

rac-16,16-Dimethyl-8-aza-17-thia-*D*-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIIa). A mixture of 131 mg of 3,4-dihydroisoquinoline (**Ia**) and

200 mg of 3-acetylthiopyran-2,4-dione (**II**) in 5 ml of ethanol was boiled under reflux for 24 h. The reaction was monitored by TLC. On completion of the reaction the mixture was left standing in the cold for crystallization of the product. The separated crystals were filtered off, washed with cold ethanol on the filter, and recrystallized from boiling ethanol. We obtained 171 mg (54.5%) 8-aza-17-thia-*D*-homo-

gonane (**IIIa**) as colorless prismatic crystals, mp 227–228°C. IR spectrum, cm^{-1} : 3000–2830, 1680, 1592, 1528, 1502, 1447, 1321, 1300, 770, 760. UV spectrum, λ_{max} , nm (ϵ): 273.8 (17950), 315.3 (22610); λ_{min} , nm (ϵ): 236.5 (5965), 288.8 (11485). Found, %: C 69.01, 68.87; H 6.06, 6.20; N 4.32, 4.40; S 10.17, 10.31. $\text{C}_{18}\text{H}_{19}\text{NO}_2\text{S}$. Calculated, %: C 68.98; H 6.11; N 4.47; S 10.23. *M* 313.42.

rac-16,16-Dimethyl-2,3-dimethoxy-8-aza-17-thia-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (**IIIb**) was obtained in the similar way from 191 mg of 3,4-dihydroisoquinoline (**Ib**) and 200 mg of 3-acetylthiopyran-2,4-dione (**II**). We obtained 242 mg (65%) of 8-aza-17-thia-D-homogonane (**IIIb**) as colorless crystals, mp 259–261°C (decomp.). IR spectrum, cm^{-1} : 3030–2830, 1682, 1623, 1600, 1545–1505, 1480–1440, 1368, 1340–1300, 1265, 1230, 1120, 1065, 832. UV spectrum, λ_{max} , nm (ϵ): 202.4 (54055), 230.6 (13705), 275 (17700), 315.3 (19950); λ_{min} , nm (ϵ): 222.1 (12760), 246.8 (7975), 293 (13830). Found, %: C 64.25, 64.41; H 6.17, 6.19; N 3.68, 3.71; S 8.63, 8.50. $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{S}$. Calculated, %: C 64.32; H 6.21; N 3.75; S 8.59. *M* 373.47.

3,4-Dihydroisoquinolines **Ia**, **b** used as substrates were prepared along Bischler–Napiralsky reaction [9], and the 3-acetylthiopyran-2,4-dione was synthesized by procedure [10]. The reaction progress was monitored and the homogeneity of compounds **IIa**, **b** was checked by TLC on Silufol UV-254 plates, eluent chloroform–methanol, 4:1, development in UV light or with iodine vapor with subsequent calcination at 250–350°C. The melting point were determined on Boetius heating block. IR spectra were registered on UR-20 instruments from KBr pellets.

UV spectra were recorded on spectrophotometer Specord M-400 in ethanol.

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