Russian Journal of General Chemistry, Vol. 72, No. 6, 2002, pp. 986–987. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 6, 2002, pp. 1053–1054.

LETTERS TO THE EDITOR

8-Aza-16-thia-D-homogona-1,3,5(10),13-tetraene-12,17*a*-diones. Annelation of 3,4-Dihydroisoquinolines by 4-acetyltetrahydro-2*H*-thiopyrane-3,5-dione

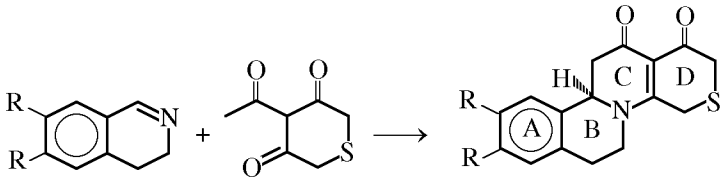
M. V. Budnikova, T. A. Zheldakova, A. L. Mikhal'chuk, and D. B. Rubinov

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, Belarus

Received August 7, 2001

Annelation of partially or exhaustively hydrogenated carbo- and heterocycles or polycyclic fragments to certain molecular frames is used in constructing polynuclear molecular skeletons of steroids or their heteroanalogs [1], alkaloids [2], and other compounds [3]. One of the most effective among such synthetic approaches to condensed nitrogenous heterocycles (azines) is annelation (cyclocondensation) of cyclic Schiff bases or azomethines by β-dicarbonyl compounds or their derivatives [4, 5]. The syntheses of 8-azasteroids and their derivatives with additional heteroatoms in other positions of the ABCD tetracyclic steroid skeleton, based on such approaches [6, 7], provide wide possibilities for preparing new compounds for physicochemical and medicobiological studies.

We made use of the above approach to prepare from 3,4-dihydroisoquinolines **Ia**, **Ib** and 4-acetyltetrahydro-2*H*-thiopyrane-3,5-dione (**II**) new azathia steroids **IIIa**, **IIIb** which present theoretical and practical interest in terms of development of new means for controlling human and animal immunity [8]. The condensations of 3,4-dihydroisoquinolines **Ia**, **Ib** with β,β'-triketone **II** were accomplished by keeping equimolar reactant mixtures in alcohol solutions at room temperature. The reactions were complete within 6 h, and the target products were isolated as crystalline precipitates. It is noteworthy that, regardless of mild reaction conditions, we could not observe (TLC) formation of any intermediate products. This is evidence showing that the reaction involves not successive formation of C–C and C–N bonds followed by dehydration of the hypothetical intermediate alcohol [4], but as a single concerted electron redistribution that yields directly compounds **IIIa**, **IIIb**.



Ia, Ib + **II** → **IIIa, IIIb**

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

The above result presents both theoretical and practical interest, demonstrating a biogenetically-like annelation, opening ways to new heteroatomic steroid analogs, and extending the substrate basis of annelation of cyclic Schiff bases by polyketides and their enol derivatives.

Convincing evidence for the structure of compounds **IIIa**, **IIIb** comes, along with elemental analysis data, confirmatory of the brutto formulas of the compounds, and IR and UV spectral data which reveal the presence of an $N^8–C^{14}=XC^{13}(–C^{12}=O)–C^{17a}=O$ fragment [5], from the ^1H NMR spectra

1070-3632/02/7206-0986 $27.00

which contain an *ABX* spin system (H^9, $H^{11A,B}$) characteristic of one of the key fragments of 8-aza-D-homogonane structures [5, 8].

8-Aza-16-thia-D-homogona-1,3,5(10),13-tetraene-12,17*a*-dione (IIIa). A mixture of 0.13 g of 3,4-dihydroisoquinoline **Ia** and 0.14 g of β,β'-triketone **II** in 5 ml of ethanol was left to stand for 6 h at room temperature. Crystals formed and were filtered off and recrystallized from ethanol to obtain 0.22 g (78%) of compound **IIIa** as white crystals, mp 277– 279°C (decomp.). IR spectrum, ν, cm^{-1}: 1680, 1610, 1515, 1500, 1460, 1440, 1415, 1405, 1355, 1340, 1300, 1280, 1220, 1200, 1170, 1130, 1110, 1080, 1000, 970, 870. UV spectrum, λ_{max}, nm (ε): 270.4 (11860), 314.6 (16540); λ_{min}, nm (ε): 239.3 (5040), 286.9 (4655). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.64 d.d (1H, $C^{11}H_B$, $J_{H_BH_A}$ 16, $J_{H_BH_X}$ 4), 2.81 d.d (1H, $C^{11}H_A$, $J_{H_AH_B}$ 16, $J_{H_AH_X}$ 4), 4.93 d. d (1H, C^9H_X, $J_{H_XH_A}$ 4, $J_{H_XH_B}$ 15). Found, %: C 67.26, 67.19; H 5.28, 5.25; N 4.82, 4.87; S 11.37, 11.33. $[M]^+$ 285. $C_{16}H_{15}NO_2S$. Calculated, %: C 67.34; H 5.30; N 4.91; S 11.24. *M* 285.37.

2,3-Dimethoxy-8-aza-16-thia-D-homogona-1,3,5(10),13-tetraene-12,17*a*-dione (IIIb) was prepared in a similar way from 0.19 g of 3,4-dihydroisoquinoline **Ib** and 0.14 g of β,β'-triketone **II**. Yield 0.28 g (82%), colorless crystals, mp 259—261°C (decomp.). IR spectrum, ν, cm^{-1}: 1680, 1620, 1520, 1510, 1470, 1440, 1380, 1350, 1300, 1270, 1220, 1160, 1125, 1080, 1035. UV spectrum, λ_{max}, nm (ε): 201.9 (63580), 230 (14310), 275.4 (15570), 314.3 (18945); λ_{min}, nm (ε): 223.1 (13990), 248.5 (6870), 291.6 (14470). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.39 d.d (1H, $C^{11}H_B$, $J_{H_BH_A}$ 15.5, $J_{H_BH_X}$ 15.0), 2.63 d.d (1H, $C^{11}H_A$, $J_{H_AH_B}$ 15.5, $J_{H_AH_X}$ 3.5), 4.82 d.d (1H, C^9H_X, $J_{H_XH_A}$ 3.5, $J_{H_XH_B}$ 15.0). Found, %: C 62.51, 62.64; H 5.42, 5.45; N 3.93, 4.01; S 9.40, 9.33. $[M]^+$ 345. $C_{18}H_{19}NO_4S$. Calculated, %: C 62.59; H 5.54; N 4.06; S 9.28. *M* 345.42.

The IR spectra were obtained on a UR-20 instrument in KBr pellets. The UV spectra were taken on a Specord M-400 spectrophotometer for alcohol solutions. The ^1H NMR spectra were obtained on a Bruker AC-200 instrument (200 MHz), internal reference TMS. The mass spectra were registered on a Shimadzu-MS QP-5000 mass spectrometer, direct inlet, ionizing energy 70 eV. The reaction progress and the purity of the products were controlled by TLC on Silufol UV-254 plates, eluent chloroform–methanol, 9:1, development in UV light or by spaying with a ferric chloride solution. The melting points were measured on a Boetius hot stage.

REFERENCES

1. Akhrem, A.A. and Titov, Yu.A., *Total Steroid Synthesis*, New York: Plenum, 1970.
2. Akhrem, A.A., Moiseenkov, A.M., Malishevskii, V.S., and Chernov, Yu.G., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1973, no. 6, p. 1308.
3. Weinreb, S.M. and Staib, R.R., *Tetrahedron*, 1982, vol. 38, no. 21, p. 3087.
4. Von Strandtmann, M., Cohen, M.P., and Shavel, J., Jr., *J. Org. Chem.*, 1966, vol. 31, no. 3, p. 797.
5. Gulyakevich, O.V., Mikhal'chuk, A.L., Verenich, A.I., Rubinov, D.B., Zenyuk, A.A., and Akhrem, A.A., *Enaminy v organicheskom sinteze* (Enamines in Organic Synthesis), Ekaterinburg: Ural Otd. Ross. Akad. Nauk, 1996, p. 111.
6. Gulyakevich, O.V., Mikhal'chuk, A.L., Peresada, V.P., Likhosherstov, A.M., and Akhrem, A.A., *Zh. Obshch. Khim.*, 1993, vol. 63, no. 3, p. 701.
7. Budnikova, M.V., Rubinov, D.B., Lis, L.G., and Mikhal'chuk, A.L., *Mendeleev Commun.*, 1999, no. 5, p. 208.
8. Konoplya, N.A., Gulyakevich, O.V., Mikhal'chuk, A.L., and Kuz'mitskii, B.B., *Vestsi Akad. Navuk Belarusi, Ser. Khim. Navuk*, 1994, no. 3, p. 91.