Chemistry of Heterocyclic Compounds, Vol. 39, No. 7, 2003

INVESTIGATION OF THE REGIO- AND STEREOCHEMISTRY OF THE [2+4] CYCLO-CONDENSATION OF 3,4-DIHYDROISOQUINOLINES WITH 2-ACETYL-4-HYDROXYCYCLOHEXANE-1,3-DIONE. SYNTHESIS AND PROPERTIES OF THE REGIOISOMERIC 15- AND 17-HYDROXY DERIVATIVES OF 8-AZA-D-HOMOGONA-12,17a-DIONES

O. V. Gulyakevich, V. G. Zaitsev, and A. L. Mikhal'chuk

The 15- and 17-hydroxy derivatives of 8-aza-D-homogona-12,17a-diones were obtained by the annelation of 3,4-dihydroisoquinolines with 2-acetyl-4-hydroxycyclohexane-1,3-dione. It was shown that the reaction proceeds stereoselectively with the intermediate formation of 9,15- and 9,17-trans isomers. The probable mechanism and certain aspects of the interconnection between the structural and physicochemical characteristics of the obtained compounds are discussed.

Keywords: azomethines, 2-acetyl-4-hydroxycyclohexane-1,3-dione, 3,4-dihydroisoquinolines, Schiff's bases, β,β'-triketones, annelation, regiochemistry, stereochemistry, cyclocondensation.

Investigations of the regio- and stereochemistry of annelation reactions of cyclic Schiff's bases (azomethines) with β-di- and β,β'-tricarbonyl compounds are of significant theoretical interest and have an important practical value for developing purpose-directed methods for the regio- and stereospecific synthesis of condensed nitrogen-containing heterocycles. The discovery of compounds with immuno-modulating activity in a series of 8-azasteroids obtained with the aid of such reactions imparts particular importance to this investigation [1,2]. As was shown previously [3-5], the annelation of 3,4-dihydroisoquinolines with unsymmetrical β,β'-triketones is effected regio- and stereoselectively, which enables prediction of a possible enantioselective synthesis of 8-azasteroids using enantiomeric 4-substituted 2-acetylcycloalkane-1,3-diones. However the results mentioned were obtained for a small number of 4-substituted derivatives of 2-acetyldimedone [3-5], and also for 4-acetoxy-2-acetylcyclohexane-1,3-dione [6,7], and an open question remains as to the regio- and stereoselectivity of this reaction when applied to other unsymmetrical derivatives of β,β'-triketones of the cyclopentane and cyclohexane series. Extension of the considered reaction to the now available 2-acetyl-4-hydroxycyclohexane-1,3-dione [8] showed that, in difference to the examples reported previously, a mixture is formed in the present case of the regioisomeric 15- and 17-hydroxy derivatives of 8-aza-D-homogona-12,17a-diones [9]. Such a result raised the possibility of the synthesis of regioisomeric hydroxy derivatives of

---

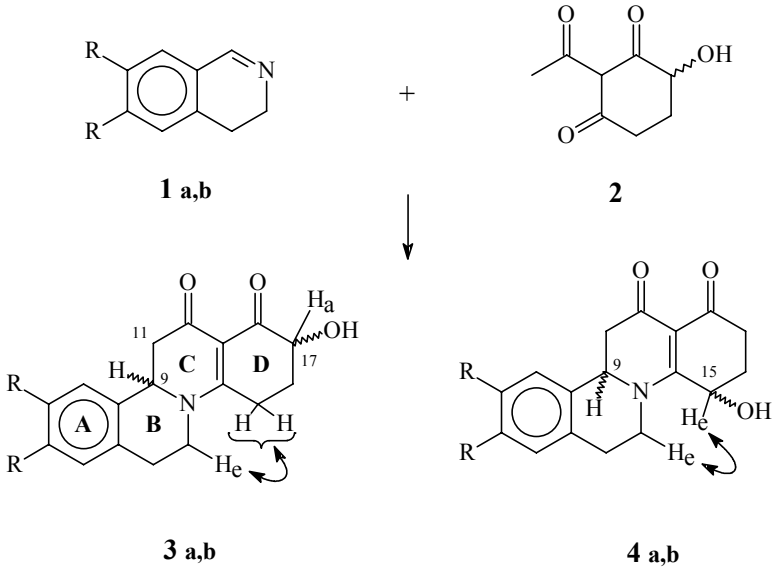
Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk 220141; e-mail: rubinov@ns.iboch.ac.by. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1043-1052, July, 2003. Original article submitted October 29, 2000; revision submitted June 14, 2001.

0009-3122/03/3907-0901$25.00

8-azasteroids, which are available with difficulty within the framework of known synthetic methods, for medico-biological investigations and structure–function correlations. This required a more detailed investigation of the regio- and stereochemistry of the annelation of 3,4-dihydroisoquinolines with 2-acetyl-4-hydroxycyclohexane-1,3-dione.

The 3,4-dihydroisoquinolines used in the present work were obtained by the Bischler–Napieralski reaction [10] by the cyclodehydration of the appropriate phenethylamides. In the case of compound **1a** this was by the action of polyphosphoric acid, for **1b** phosphorus oxychloride, and for β,β'-triketone **2** by the method of [8].

Scheme 1



1, **3**, **4 a** R = H; **b** R = OMe

The condensation of cyclic azomethines **1a,b** with β,β'-triketone **2** was effected either by refluxing equimolar mixtures of the reactants in ethanol, or by maintaining them at room temperature (15-20°C). It was established that irrespective of the reaction conditions two chromatographically different substances are formed, and were isolated in a pure state. According to data of elemental analysis (Table 1) the obtained compounds have the empirical composition of tetracyclic cyclocondensation products. As a result of physicochemical investigations the structure of the regioisomeric 15- and 17-hydroxy derivatives **3a,b** and **4a,b** respectively were ascribed to them. According to the data of the spectral investigations the chromatographically homogeneous (Silica gel F_{60} 254, chloroform–methanol, 8:2) regioisomeric alcohols **3a,b** and **4a,b** are mixtures (~20:80 according to ^{1}H NMR data) of the *cis* and *trans* isomers with a predominance of the latter.

The results of NMR spectroscopy are most informative for clarifying the structure and stereochemistry of the products obtained. In the ^{1}H NMR spectra of compounds **3a,b** and **4a,b** (Table 2) resonance signals were present for an ABX spin system for the position 9 and 11 protons characteristic of 8-aza-D-homogona-12,17a-diones [4,5] , showing, according to the Karplus principle [11], the quasiaxial disposition of the 9-H proton ($J_{9\text{-Ha},11\text{-Ha}}$ = 15, $J_{9\text{-Ha},11\text{-He}}$ = 5 Hz). The resonance signals for the protons of the $C_{(6)}$–$C_{(7)}$ fragment indicate the rigidly fixed *boat* conformation for ring B. The signals of the quasiequatorial protons in position 7 of alcohols **3a,b** are displaced by 0.5 ppm towards high field relative to the signals of the protons of the analogous alcohols **4a,b**. Such a difference in chemical shift is caused by the anisotropic influence of the 15-OH group in compounds **4a,b**. On the other hand the proton signals of the carbon atoms connected to a hydroxyl group are

TABLE 1. Physicochemical Characteristics of 8-Aza-D-homogona-12,17a-diones **3a,b** and **4a,b**

Compound	Empirical formula	Found, % / Calculated, %			$[M]^+$	M	R_f	mp, °C*	Yield*[2], %
		C	H	N					
3a	$C_{17}H_{17}NO_3$	72.07 / 72.07	6.05 / 5.77	4.94 / 4.80	283	283.33	0.74	184-186	50 (46.4)
3b	$C_{19}H_{21}NO_5$	66.47 / 66.21	6.16 / 6.14	4.08 / 4.02	343	343.38	0.66	222-223	30.6
4a	$C_{17}H_{17}NO_3$	72.07 / 72.15	6.05 / 5.97	4.94 / 4.71	283	283.33	0.63	186-189	43 (46.4)
4b	$C_{19}H_{21}NO_5$	66.47 / 66.21	6.16 / 6.16	4.08 / 3.97	343	343.38	0.58	197-199	43.7

* All substances melted with decomposition.

*[2] The yield on carrying out the reaction without heating is given in parentheses.

shifted in alcohols **4a,b** towards low field by 0.8-0.9 ppm relative to the corresponding signals for alcohols **3a,b**, which indicates a significant difference in the electronic environment of these protons. Such a difference is probably due to the anisotropic effect of the strongly polarized $C_{(14)}$=$C_{(13)}$ bond in the case of compounds **4a,b**. A similar difference in proton chemical shifts of the CH carbon of fragments CH–OH was observed previously in the case of 4-hydroxycyclohex-2-enone and 6-hydroxy-3-methoxycyclohex-2-enone [12]. It is important to note that the signals of the 17-H protons of alcohols **3a,b** are displayed as a doublet of doublets with coupling constants J = 5 and J = 12-13 Hz. This indicates the quasiaxial disposition of the protons mentioned. At the same time, the signals of the 15-H protons of alcohols **4a,b** are observed as triplets (J = 5.0 Hz), indicating their quasiequatorial disposition. Study of the nuclear Overhauser effect showed the presence of long-range spin-spin interactions between the 7-H and 15-H protons in compounds **4a,b** and between the 7-H_e protons and the methylene protons at $C_{(15)}$ located at 2.7-3.3 ppm for compounds **3a,b**.

The 15-hydroxy derivatives **4a,b** were poorly soluble in chloroform and alcohols compared with the 17-hydroxy derivatives **3a,b**, but were moderately soluble in pyridine. Consequently the NMR spectra of some of the indicated compounds were obtained in pyridine-d_5.

The number and type of resonance signals of the ^{13}C atoms appropriate to the assigned structure were present in the ^{13}C NMR spectra of aza-D-homogonadiones **3a,b** and **4b** (see Experimental). Both for diones **3a,b** and also for diones **4a,b** there were low intensity companions for individual signals in the ^1H and ^{13}C NMR spectra, the presence of which points to the presence of a second isomer in each case, *viz*. *cis*-$C_{(9)}$,$C_{(17)}$ for compounds **3** and *cis*-$C_{(9)}$,$C_{(15)}$ for compounds **4**.

In the IR spectra of products **3a,b** and **4a,b** (Table 3) absorption bands were present in the 1400-1700 cm^{-1} region characteristic of the vibrations of the α-acyl-β-aminovinylcarbonyl (AAVC) fragment $N_{(8)}$–$C_{(14)}$=$C_{(13)}$ (–$C_{(12)}$=O)–$C_{(17)}$=O and the C=C bonds of the aromatic ring A [4], confirming the presence of the tetracyclic 8-aza-D-homogona-12,17a-dione structure. Broad bands were observed at 3300-3600 cm^{-1} caused by the presence of hydroxyl groups. It is interesting that the absorption bands for the stretching vibrations of the carbonyl groups of diones **3a,b** (at 1685-1690 cm^{-1}) were displaced to higher frequencies, compared with the analogous bands for diones **4a,b** (at 1670-1680 cm^{-1}). This difference, explained by the different structure of compounds **3** and **4**, may be used for structural assignments.

TABLE 2. ^{1}H NMR Spectra of Compounds **2**, **3a,b**, and **4a,b**

Compound	Solvent	Chemical shifts, δ, ppm (coupling constant, *J*, Hz)
1	2	3
2	$CDCl_3$	1.84 (1H, dddd, J_1 = 3.0, J_2 = 8.0, J_3 = J_4 = 13.0, 5-H_a); 2.40 (1H, dddd, J_1 = 2.5, J_2 = 4.0, J_3 = 5.5, J_4 = 13.0, 5-H_e); 2.64 (3H, s, CH_3); 2.81 (2H, m, 4,4-H_2); 4.03 (1H,d, J = 1.0, 6-OH); 4.10 (1H, ddd, J_1 = 1.0, J_2 = 5.5, J_3 = 13.0, 6-H); 18.14 (1H, s, H_{enol})
2	Py-d_5	1.93 (1H, m, J_1 = J_2 = 12.0, J_3 = 5.0, J_4 = 8.5, 5-H_a); 2.28 (1H, qq, J_1 = 5.0, J_2 = 12.0, 5-H_e); 2.62 (3H, s, CH_3CO); 2.72 (2H, dd, J_1 = 5.0, J_2 = 8.5, 6-H_2); 4.33 (1H, dd, J_1 = 5.0, J_2 = 12.0, 4-H_a)
[7-^{2}H] isotopomer of **2**	Py-d_5+D_2O	1.86 (1H, t, J_1 = J_2 = 12.5, 5-H_A); 2.33 (1H, dd, J_1 = 5.0, J_2 = 12.5, 5-H_B); 4.25 (1H, dd, J_1 = 5.0, J_2 = 12.5, 4-H_a)
[8-^{2}H] isotopomer of **2**	Py-d_5+D_2O	1.86 (1H,d, J_{AB} = 12.5, 5-H_A); 2.34 (1H, dd, J_{BA} = 12.5, 5-H_B)
3a	$CDCl_3$	1.82 (1H, m, J_1 = 5.5, J_2 = J_3 = J_4 = 13.0, 16-H_a); 2.36-2.52 (1H, m, 16-H_e); 2.60 (1H, t, J = 16.0, 11-$H_{B(a)}$); 2.74-3.26 (4H, m, 6-H_a, 6-H_e, 15,15-H_2); 2.86 (1H, dd, J_1 = 4.0, J_2= = 16.0, 11-$H_{A(e)}$); 3.44 (1H,dtd, J_1 = 4.0, J_2 = 10.0, J_3 = 13.0, 7-H_a); 3.94 (1H, dd, J_1 = 5.0, J_2 = 13.0, 17-H_a); 4.26 (1H, tt, J_1 = J_2 = 4.0, J_3 = 13.0, 7-H_e); 4.39 (1H, br. s, 17-OH (deuterium exchange)); 4.94 (1H, dd, J_1 = 4.0, J_2 = 16.0, 9-$H_{X(a)}$); 7.10-7.40 (4H, m, 1-, 2-, 3-, 4-H). Minor signal: 4.04 (dd, J_1 = 5.0, J_2 = 13.0, 17-H_a)
3b	$CDCl_3$	1.82 (1H,dq, J_1 = 5.0, J_2 = J_3 = J_4 = 13.0, 16-H_a); 2.50 (1H, m, 16-H_e); 2.60 (1H, t, J_{BA} = 14.5, 11-$H_{B(a)}$); 2.72-3.20 (5H, m, 6-H_a, 6-H_e, 11-$H_{A(e)}$, 15,15-H_2); 2.92 (1H, br. s, 17-OH (deuterium exchange)); 3.42 (1H, br. q, J = 11.0, 7-H_a); 3.87 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 4.00 (1H, dd, J_1 = 5.0, J_2 = 13.0, 17-H_a); 4.27 (1H, br. t, J = 11.0, 7-H_e); 4.88 (1H, dd, J_1 = 3.5, J_2 = 14.5, 9-$H_{X(a)}$); 6.64 (1H, s, 4-H); 6.70 (1H, s, 1-H). Minor signal: 4.04 (dd, J_1 = 5.0, J_2 = 13.0, 17-H_a)
3b	Py-d_5	1.38 (1H, br. s, 17-OH (deuterium exchange)); 1.90 (1H, m, 16-H_a); 2.41 (1H, m, 16-H_e); 2.54-2.86 (3H, m, 6-H_e, 11-$H_{B(a)}$, 15-H); 2.86-3.15 (3H, m, 6-H_a, 11-$H_{A(a)}$, 15-H); 3.22 (1H, m, 7-H_a); 3.78 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 4.13 (1H, tt, J_1 = J_2 = 3.0, J_3 = 14.0, 7-H_e); 4.17 (1H, dd, J_1 = 5.0, J_2 = 12.0, 17-H_a); 4.90 (1H, br. dd, J_1 = 4.0, J_2 = 13.0, 9-$H_{X(a)}$); 6.81 (1H, s, 4-H), 6.87 (1H, s, 1-H)
4a	$CDCl_3$	1.62-1.96 (2H, m, 16,16-H_2); 1.96-2.34 (2H, m, 17,17-H_2); 2.56 (1H, t, J = 15.0, 11-$H_{B(a)}$); 2.74 (1H, dd, J_1 = 4.0, J_2 = 15.0, 11-$H_{A(e)}$); 3.02 (1H, tt, J_1 =J_2 = 3.5, J_3=12.0, 6-H_e); 3.48 (1H, br. s, 15-OH (deuterium exchange)); 3.48 (1H,dtd, J_1 = 3.5, J_2 = 12.0, J_3 = 15.0, 6-H_a); 3.70 (1H,dtd, J_1 = 3.5, J_2 = 13.5, J_3 = 15.0, 7-H_a); 4.53 (1H, tt, J_1 = J_2 = 3.5, J_3 = 13.5, 7-H_e); 4.90 (1H, t, J_1 = J_2 =5.0, 15-H_e); 4.96 (1H, dd, J_1 = 4.0, J_2=15.0, 9-$H_{X(a)}$); 7.09-7.36 (4H, m, 1-, 2-, 3-, 4-H). Minor signals: 4.28 (dd, J_1 = 5.0, J_2 = 12.0, 17-H_a); 4.83 (dd, J_1 = 4.0, J_2 = 13.0, 9-$H_{X(a)}$); 6.79 (s, 4-H); 6.85 (s, 1-H)
4a	Py-d_5	2.23 (2H, q, J = 5.0, 16,16-H_2); 2.46 (1H, dd, J_1 = 5.0, J_2 = 16.0, 17-H_e); 2.53 (1H, t, J_1 = J_2 =14.0, 11-$H_{B(a)}$); 2.74 (1H, tt, J_1 = J_2 = 3.5, J_3 = 12.0, 6-H_e); 2.88 (1H, dd, J_1 = 4.0, J_2 = 14.0, 11-$H_{A(e)}$); 3.01 (1H, dd, J_1 = 5.0, J_2 = 16.0, 17-H_a); 3.10 (1H, ddd, J_1 = 3.5, J_2 = J_3 =12.0, 6-H_a); 3.32 (1H, ddd, J_1 = 3.5, J_2 = J_3 =12.0, 7-H_a); 4.79 (1H, tt, J_1 = J_2 = 3.5, J_3 = 12.0, 7-H_e); 4.91 (1H, dd, J_1 = 4.0, J_2 = 14.0, 9-$H_{X(a)}$); 4.96 (1H, t, J_1 = J_2 = 5.0, 15-H_e); 7.02-7.35 (4H, m, 1-, 2-, 3-, 4-H)

TABLE 2 (continued)

1	2	3
4b	$CDCl_3$	2.18 (2H, m, 16,16-H_2); 2.48-2.76 (3H, m, 6-H_e, 11-$H_{B(a)}$, 17-H_e); 2.86 (1H, dd, J_1 = 4.0, J_2 = 15.0, 11-$H_{A(e)}$); 2.94-3.52 (3H, m, 6-, 7-, 17-H_a); 3.86 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 4.68-4.97 (3H, m, 7-H_e, 9-$H_{X(a)}$, 15-H_e; 6.60 (1H, s, 4-H); 6.70 (1H, s, 1-H). Minor signals: 3.88 (s, OCH_3); 6.68 (s, 1-H)
4b	Py-d_5	1.38 (1H, br. s, 15-OH (deuterium exhange)); 2.26 (2H, m, 16,16-H_2); 2.44 (1H, tt, J_1 = 5.0, J_2 = J_3 = 15.0, 17-H_a); 2.58 (1H, t, J_1 = J_2 = 15.0, 11-$H_{B(a)}$); 2.78 (1H, tt, J_1 = 4.0, J_2 = 4.0, J_3 = 12.0, 6-H_e); 2.95 (1H, dd, J_1 = 4.0, J_2 = 15.0, 11-$H_{A(e)}$); 3.04 (1H, tt, J_1 = J_2 = 5.0, J_3 = 15.0, 17-H_e); 3.12 (1H,d. t.d, J_1 = 4.0, J_2 = J_3 = 12.0, 6-H_a); 3.36 (1H, ddd, J_1 = 4.0, J_2 = J_3 = 12.0, 7-H_a); 3.85 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 4.78 (1H, tt, J_1 = J_2 =4.0, J_3 = 12.0, 7-H_e); 4.88 (1H, dd, J_1 = 4.0, J_2 = 15.0, 9-$H_{X(a)}$); 4.99 (1H, t, J_1 = J_2 = 5.0, 15-H_e); 6.77 (1H, s, 4-H); 6.88 (1H, s, 1-H). Minor signals: 3.80 (s, OCH_3); 6.79 (s, 4-H); 6.83 (s, 1-H)

TABLE 3. IR and UV Spectra of Compounds **3a,b** and **4a,b**

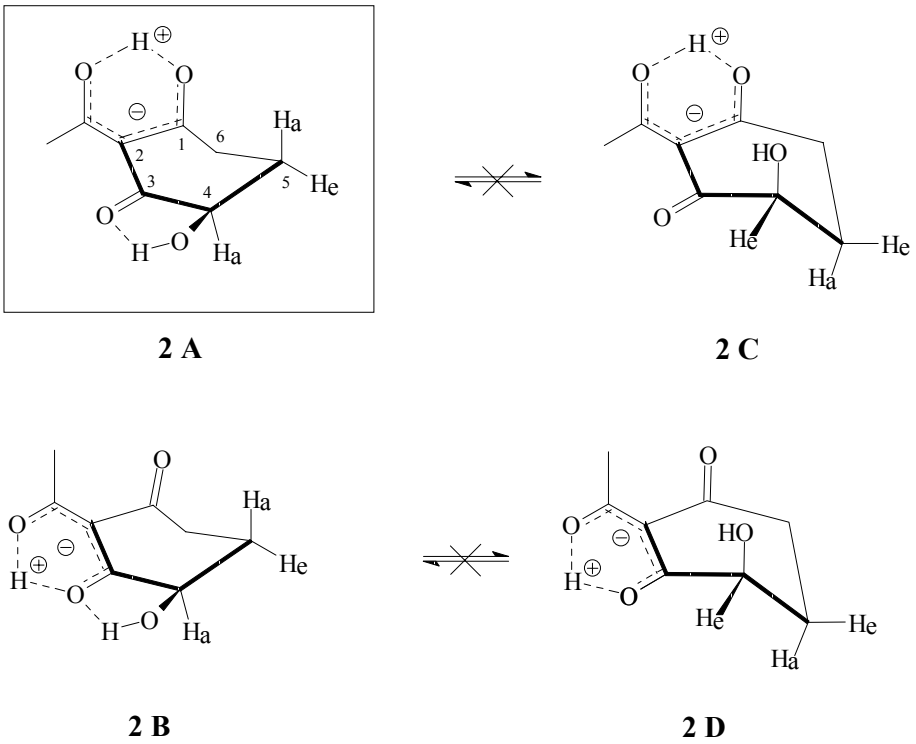
Com-pound	IR spectrum, ν, cm^{-1}	UV spectrum, λ, nm (log ε)	
		λ_{max}	λ_{min}
3a	3600-3300, 3000-2800, 1685, 1645, 1619, 1592, 1540-1510, 1500 sh., 1460, 1418, 1345-1305, 1158, 1121, 1092, 1024, 991, 886, 780	225 (2.97), 265 (4.21), 303.9 (4.30)	230.8 (2.88), 279.6 (4.01)
3b	3600-3300, 3000-2830, 1685, 1618, 1550-1510, 1455, 1426, 1370, 1340, 1322, 1261, 1232, 1210, 1157, 1131, 1111, 1025, 995, 868, 817, 771	230 (4.01), 266.6 (4.20), 303.1 (4.26)	219.3 (3.97), 245 (3.82), 278 (4.12)
4a	3600-3300, 3000-2830, 1672, 1630 sh., 1595, 1501, 1380 sh., 1362, 1338, 1199, 1158, 1078, 969, 774, 759	221.9 (3.02), 265 (4.06), 311.6 (4.18)	231.2 (2.89), 281.9 (3.74)
4b	3600-3300, 3050-2830, 1680, 1619, 1596, 1550-1505, 1480-1445, 1360, 1340, 1265, 1225, 1198, 1128, 1072, 780	230.4 (4.06), 267.3 (4.20), 311.9 (4.25)	221.9 (4.03), 245.4 (3.85), 281.9 (4.05)

In the UV spectra of diones **3a,b** and **4a,b** two intense absorption maxima were present at 265-267 and 303-312 nm characteristic for the AAVC fragment of 8-aza-D-homogonanes [4] (Table 3). The long-wave maximum of compounds **4a,b** was displaced bathochromically by 8-9 nm relative to the analogous maximum of compounds **3a,b**, which reflects the structural differences of the products indicated and may be used for structural assignments. It is important to note that both maxima for compounds **3a,b** and for **4a,b** are broadened, but the long wave maximum was asymmetric in both cases. Differential resolution of the spectral curves into individual components showed that the long-wave maxima consist of two bands at 295.4 and 316.6 (**3a**), 292.3 and 311.6 (**3b**), 298.0 and 320.0 (**4a**), and 293.2 and 316.6 (**4b**), and the short-wave maxima have the following refined values: 255.4 (**3a**), 263.5 (**3b**), 257.7 (**4a**), and 265.0 nm (**4b**).

It should be noted that an absorption was also observed at ~202 and ~230 nm in the UV spectra of compounds **3a,b** and **4a,b**, which is caused by the electronic transitions in the aromatic ring.

To explain the regio- and stereochemical results and to establish the mechanism of this reaction we have studied the structure, conformation, and prototropy of 2-acetyl-4-hydroxycyclohexane-1,3-dione (**2**). The structure and conformation of 3,4-dihydroisoquinolines **1a,b** were studied and discussed previously in [7].

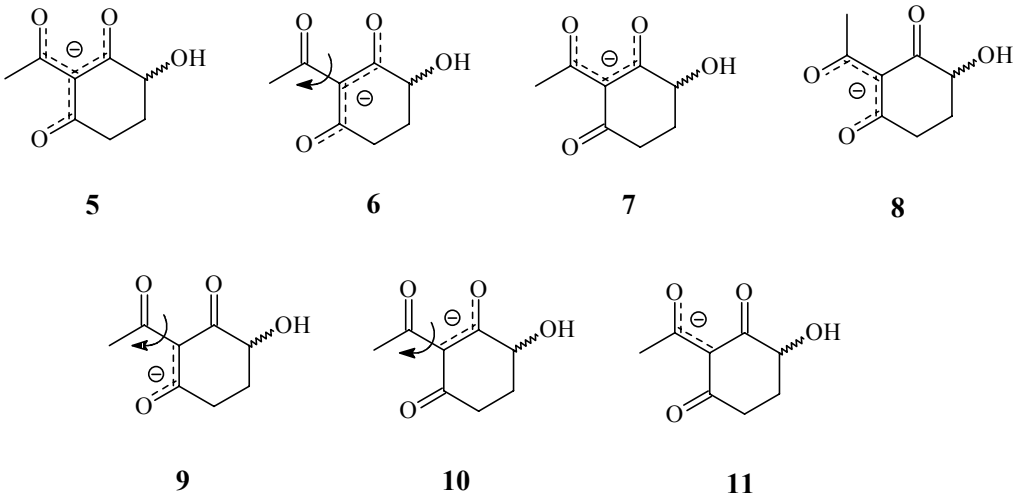
Scheme 2



Analysis of the structure of compound **2** with Dreiding models showed that (in the cases of both 4-acetoxy-2-acetylcyclohexane-1,3-dione [7] and the prochiral 5-substituted 2-acetylcyclohexane-1,3-diones [13]) the cyclohexane-1,3-dione fragment, due to the complete enolization of the β,β'-tricarbonyl grouping, and theoretically may form two *boat* conformations passing over into one another with equatorial (A, B) or axial (C, D) disposition of the hydroxyl group (see Scheme 2 for the *R*-isomer). Investigation by NMR showed that β,β'-triketone **2** in $CDCl_3$ solution, in difference to other unsymmetrical cyclohexane β,β'-triketones [3,4], is characterized exclusively by one set of resonance signals. It may be concluded from this that it forms only one of the two theoretically possible (A or B) chelated tautomers, and secondly that conformational conversions A → C or B → D are not observed. Analysis of the vicinal coupling constants of the 4-H proton with the methylene protons in position 5 ($J_{4\text{-Ha},5\text{-Ha}}$ = 13, $J_{4\text{-Ha},5\text{He}}$ = 5.5 Hz) indicate that a *boat* conformation with an equatorial disposition of the hydroxyl group (A, B) exists for β,β'-triketone **2**. Considering these data and the circumstance that a weak hydrogen bond involving the hydroxyl group is observed in the IR spectra of triketone **2** (the absorption band of a chelated proton is as a rule not displayed in the spectrum), which is more characteristic of tautomer A, it is possible to affirm that this triketone exists exclusively in form A in neutral aprotic solvents.

In solution in the proton-accepting pyridine-d_5 only one set of proton signals is observed for β,β'-triketone **2**, corresponding to the anion of this triketone. In accordance with the existing concept of the mesomeric structure of anions of carbonyl, β-di- and β,β'-tricarbonyl compounds [14] it is possible to assume heptade (5), pentade (6-8), and triade (9-11) mesomeric structures for the anion of β,β'-triketone **2** (see Scheme 3). The thermodynamically most preferable is the pentade structure of anion **6**, although the possibility is not excluded of the existence of other of the structures indicated in the experimental conditions described.

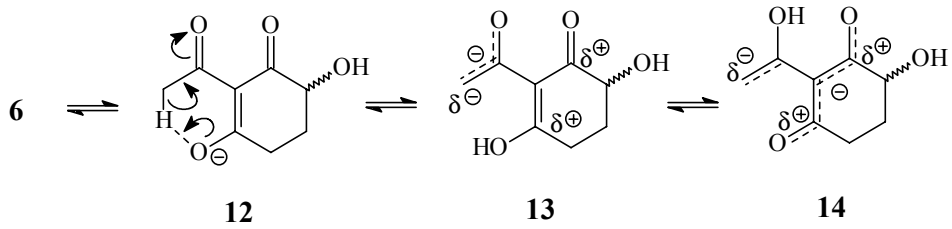
Scheme 3



5 **6** **7** **8**

9 **10** **11**

Scheme 4

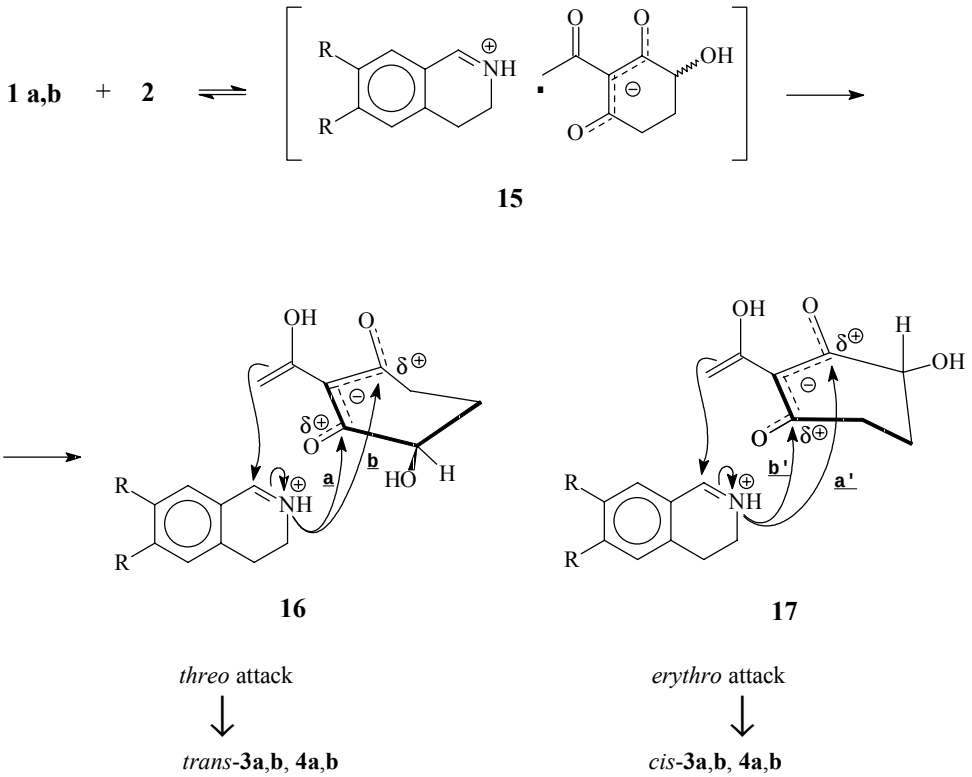


12 **13** **14**

Investigation of the isotopic exchange of β,β'-triketone **2** showed that in $CDCl_3$ solution only the hydroxyl and chelated protons were subject to H/D isotopic exchange (D_2O), but in pyridine-d_5 solution the acetyl group protons also exchanged. An analogous exchange of protons of an acetyl substituent was observed previously for salts of acetylcyclopentane-1,3-dione with 1-alkyl-3,4-dihydroisoquinolines [15] and may be explained by an "anion-enolanionic" prototropic tautomerism **6** ↔ **12** ↔ **13** ↔ **14**), which is probably general for 2-acetylcycloalkane-1,3-diones.

These concepts explaining the results of the H/D isotopic exchange in the acyl fragment of β,β'-triketone **2**, on the other hand, reveal the 1,4-dipolar nature of tautomers **13** and **14** of the β,β'-tricarbonyl fragment in reactions with dipoles of $^{\delta+}C=N^{\delta-}$ polarized bonds of Schiff's bases. In reality, on reacting triketone **2** which is an acid, with 3,4-dihydroisoquinolines **1a,b** displaying basic properties, the salts **15** are formed initially. From the latter, in accordance with the point of view expressed previously [7,13], the tetracyclic derivatives **3a,b** and **4a,b** are obtained through the six-membered transition states **16** and/or **17**. On forming the C–N bond in the direction **a**, **a'** the 15-hydroxy derivatives **4a,b** are formed, and in the direction **b**, **b'** the 17-hydroxy derivatives **3a,b** are formed. On forming the 8-aza-D-homogonane C ring through transition state **16** (*threo* attack) *trans* isomers are formed, but through transition state **17** (*erythro* attack) the *cis* isomers of compounds **3a,b** and **4a,b** are formed. It is evident that *erythro* attack of the cyclohexane-1,3-dione carbonyl groups by the nitrogen atom is less preferable as a result of the steric interactions of the nitrogen atom and $C_{(7)}H_2$ group of the isoquinoline with the $C_{(5)}H_2$ link of β,β'-triketone **2** in transition state **17**, compared with the *threo* attack in transition state **16**. Consequently the *trans* isomers of compounds **3a,b** must be formed predominantly, which is in agreement with the experimental data.

Scheme 5



It should be noted that the reason for the absence of regioselectivity in the cyclocondensation under discussion, compared with previously described reactions [3-5,7], is still not clear and requires further investigation and analysis. However it may be said that annelation of 3,4-dihydroisoquinolines **1a,b** by compound **2** is effected stereoselectively and leads to a mixture of the 17- and 15-regioisomeric hydroxy derivatives of 8-aza-D-homogonanes **3a,b** and **4a,b** with a predominance of *trans* isomers.

EXPERIMENTAL

A check on the progress of reactions and the homogeneity of the products was effected by TLC on Silica gel F_{60} 254 plates, eluent was chloroform–methanol, 8:2. The melting points of products were determined on a Boetius hot stage. The IR spectra were determined on a UR-20 instrument in KBr disks. The UV spectra were recorded on a Specord M-400 spectrophotometer for solutions in methanol. The mass spectra were obtained on a Shimadzu MS QP-5000 mass spectrometer (direct insertion of samples, energy of ionizing electrons 70 eV). The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 radiospectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C). Internal standard was TMS.

9ξ,17ξ-17-Hydroxy-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (3a) and 9ξ,15ξ-15-Hydroxy-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (4a). A. A mixture of 3,4-dihydroisoquinoline **1a** (0.13 g, 1.0 mmol) and β,β'-triketone **2** (0.19 g, 1.1 mmol) in ethanol (7 ml) was refluxed for 2 h and then kept in the refrigerator for 12 h. The precipitated crystals were filtered off. The filtrate was evaporated to dryness, the residue was combined with the crystals, and the mixture obtained was dissolved in chloroform. The solution was subjected to column flash chromatography on silica gel 5/40 μ in a gradient from chloroform to chloroform–methanol (80:20). Unreacted β,β'-triketone **2** was contained in the first portion

of eluate. From the second portion of eluate, after evaporation and crystallization of the residue (ethanol–ether) alcohol **3a** (0.14 g) was obtained as pale yellow crystals (fine prisms). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 27.07, 27.53, 29.58, 44.70 (C-11); 45.20 (C-7); 57.50 (C-9); 69.52 (C-17); 106.88 (C-13); 125.84, 127.64 (signal with double integral); 128.50, 133.35, 133.77, 170.19 (C-14); 188.17; 192.10; minor signals: 26.99, 29.23, 70.01, 133.05, 134.00, 170.20, 188.35, 192.20. From the third portion of eluate alcohol **4a** (0.12 g) was obtained analogously as colorless fine needles.

B. By keeping a mixture of compound **1a** (0.13 g, 1.0 mmol) and β,β'-triketone **2** (0.19 g, 1.1 mmol) in ethanol (5 ml) at room temperature for 32 h, and subsequently treating the reaction mixture as described above, alcohol **3a** (0.13 g) and alcohol **4a** (0.13 g) were obtained and were identical to the samples synthesized by method A (absence of depression of melting point on melting a test sample of a mixture).

9ξ,17ξ-17-Hydroxy-2,3-dimethoxy-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (3b) and 9ξ,15ξ-15-Hydroxy-2,3-dimethoxy-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (4b). A mixture of 3,4-dihydroisoquinoline **1b** (0.38 g, 2.0 mmol) and β,β'-triketone **2** (0.34 g, 2.0 mmol) in ethanol (10 ml) was kept at room temperature for 12 h, then refluxed for 2 h until complete disappearance of the starting materials from the mixture (TLC). The reaction mixture was then evaporated to half volume, diluted with ether to a weak turbidity and kept at +5°C for 12 h. The substance which separated was filtered off, washed with ether, and air-dried. Crude product (0.59 g, 85.5%) was obtained and was subjected to column flash-chromatography. Alcohol **3b** (0.21 g) was obtained from the first eluate as pale yellow plates. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 27.80, 27.52, 29.20, 44.73, 45.60 (C-7); 56.03 (OCH_3); 56.13 (OCH_3); 57.30 (C-9); 69.50 (C-17); 106.79 (C-13); 108.44, 111.01, 125.34, 125.49, 148.41 (C-3); 148.64 (C-2); 170.05 (C-14); 188.26, 192.13; minor signals: 27.07, 45.12, 57.15, 70.20, 107.74, 124.90, 125.75. From the second eluate after evaporation and crystallization of the residue from an ethanol–ether mixture, alcohol **4b** (0.34 g) was obtained as colorless fine prisms. ^{13}C NMR spectrum (Py-d_5), δ, ppm: 29.60 (C-16); 32.85 (C-11); 45.96 (C-17); 46.95 (C-7); 55.91 (OCH_3); 56.16 (OCH_3); 57.81 (C-9); 63.51 (C-15); 109.35 (C-13); 110.01 (C-4); 112.12 (C-1); 126.94, 126.99, 148.97, 149.19, 169.34 (C-14); 188.74, 191.90; minor signals; 29.73, 30.44, 33.83, 46.21, 57.18, 64.34, 126.67, 127.29, 170.33, 189.00, 191.51.

REFERENCES

1. A. A. Akhrem, B. B. Kuz'mitskii, F. A. Lakhvich, V. A. Khripach, and Yu. L. Zhuravkov, *Chemistry and Biology of Immunomodulators* [in Russian], Zinatne, Riga (1985), p. 265.
2. N. A. Konoplya, O. V. Gulyakevich, A. L. Mikhal'chuk, and B. B. Kuz'mitskii, *Ves. Akad. Nauk Belarus., Ser. Khim. Navuk*, No. 3, 91 (1994).
3. 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).
4. A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov, and A. A. Akhrem, *Khim. Geterotsikl. Soedin.*, 374 (1993).
5. O. V. Gulyakevich, A. L. Mikhal'chuk, A. I. Verenich, D. B. Rubinov, A. A. Zenyuk, and A. A. Akhrem, *Enamines in Organic Synthesis* [in Russian], Urals Branch of the Russian Academy of Sciences, Ekaterinburg (1996), p. 111.
6. O. V. Gulyakevich, V. G. Zaitsev, and A. L. Mikhal'chuk, *Zh. Obshch. Khim.*, **69**, 1041 (1999).
7. O. V. Gulyakevich, V. G. Zaitsev, and A. L. Mikhal'chuk, *Khim. Geterotsikl. Soedin.*, 1092 (2000).
8. V. G. Zaitsev, G. I. Polozov, and F. A. Lakhvich, *Tetrahedron*, **50**, 6377 (1994).
9. O. V. Gulyakevich, V. G. Zaitsev, and A. L. Mikhal'chuk, *Zh. Obshch. Khim.*, **70**, 1581 (2000).
10. W. M. Whaley and T. R. Govindachari, in: *Organic Reactions*, Vol. 6, Wiley, New York (1951), p. 151.
11. M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

12. V. G. Zaitsev, D. G. Sachava, G. S. Yankovskaya, and N. I. Garbuz, *Chirality*, **12**, 287 (2000).
13. O. V. Gulyakevich, I. L. Rubinova, D. B. Rubinov, A. A. Govorova, A. S. Lyakhov, and A. L. Mikhal'chuk, *Mendeleev Commun.*, 119 (1999).
14. E. Yu. Gudriniece (editor), *Structure and Tautomeric Conversions of β-Dicarbonyl Compounds* [in Russian], Zinatne, Riga (1977).
15. A. L. Mikhal'chuk, O. V. Gulyakevich, Yu. V. Shklyaev, V. S. Shklyaev, and A. A. Akhrem, *Khim. Geterotsikl. Soedin.*, 681 (1998).