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REGIOISOMERIC ACETOXY DERIVATIVES OF 8-AZA-*D*-HOMOGONA-12,17a-DIONE. ANNELATION OF 1-METHYL-3,4-DIHYDRO-ISOQUINOLINE WITH 4-ACETOXY-2-ACETYLCYCLOHEXANE-1,3-DIONE

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Annelation ([2+4] cyclocondensation) of 1-methyl-3,4-dihydroisoquinoline with 4-acetoxy-2-acetylcyclohexane-1,2-dione leads to a mixture of regioisomeric acetoxy derivatives of 9-methyl-8-aza-D-homogona-12,17a-dione.

Keywords: 8-aza-*D*-homogonanes, 8-azasteroids, 2-acylcyclohexane-1,3-diones, 3,4-dihydroisoquinolines, cyclic Schiff's bases, annelation, regioselectivity, stereochemistry.

Annelation reactions of cyclic Schiff's bases with β-di- and β,β'-tricarbonyl compounds or their enolic derivatives is an exceptionally simple and effective approach to the construction of an ABCD tetracyclic system of steroid heteroanalogs [1-4]. The interest in compounds of such a series is caused by the appearance of biological activity [5, 6] and the prospect linked with this of developing new pharmacological agents from them for medical and veterinary use [7].

It was shown previously that cyclocondensation of 3,4-dihydroisoquinolines with 4-substituted 2-acetyldimedones and 2-acetylcyclohexane-1,3-diones is effected regio- and stereoselectively leading to the 9,17-*trans*-diastereomer of 8-aza-*D*-homogonanes [3, 8-11]. In the case of 2-acetyl-4-hydroxycyclohexane-1,3-dione mixtures are formed of the regioisomeric 15- and 17-hydroxy derivatives of 8-aza-*D*-homogonanes [12], but with 1-alkyl-substituted 3,4-dihydroisoquinolines 15-hydroxy derivatives are formed exclusively. This indicates a reverse of the regiochemistry of this reaction. The reasons for such a change on going from 4-substituted derivatives of 2-acyldimedones [3, 8, 9] to a 4-substituted derivatives of 2-acetylcyclohexane-1,3-dione [10-12] are still not completely clear. At the same time the special features of the annelation of cyclic Schiff's bases with β,β'-tricarbonyl compounds is of both practical and theoretical interest, raising the possibility of directing their regio- and stereochemical results and of obtaining new derivatives of 8-azasteroids of the required structure for physicochemical and medico-biological investigations.

In view of what has been stated it seemed important to clarify how the presence of a methyl group at the azomethine carbon atom of 3,4-dihydroisoquinoline **1** influences its annelation by 4-acetoxy-2-acetylcyclohexane-1,3-dione (**2**).

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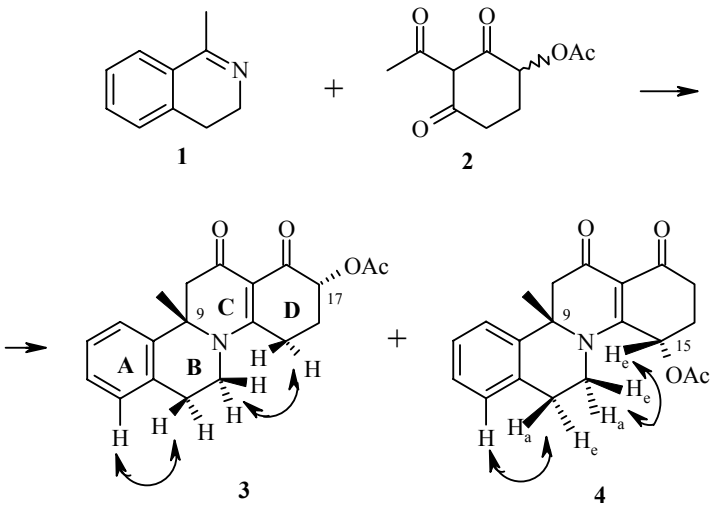


The condensations of isoquinoline **1** with triketone **2** were effected by boiling equimolar mixtures of them in alcohols or by keeping the mixtures indicated at room temperature in accordance with known conditions [8, 9]. It was shown in this way that in all the cases studied a mixture was formed of the 17- and 15-acetoxy derivatives of 8-aza-*D*-homogonanes **3** and **4** respectively in approximately the same ratio. As noted previously [2, 8, 13], the first event of the interaction of the 3,4-dihydroisoquinolines displayed basic properties with the β,β'-triketones displayed acidic properties is salt formation, which enables reactions to proceed as a result of coulombic interactions of the ionized reactants. It is evident that in this case dilution of the reaction medium must affect the reaction rate to a lesser extent than in the case of the interaction of nonionized reactants. Nonetheless a significant reduction of reaction rate on dilution was established for the interactions of azomethine **1** with β,β'-triketone **2**. Thus, for completion of the reaction at a ratio (**1** + **2**) : solvent equal to ~1:50, ~5 h is required, at a component ratio ~1:100 the reaction time amounted to ~25 h, and at a ratio ~1:200 the reaction was not complete after 72 h boiling. Such a dependence of reaction rate on the extent of dilution might be caused, in particular, by conformational and/or tautomeric conversions of the interacting compounds, when not every collision of molecules leads to the formation of products. Heating in the studied experiments therefore shows up insignificantly on the reaction rate if the ratio indicated above is ≤1:50.

According to the data obtained the acetoxy derivatives **3** and **4** were isolated as the 9,17- and 9,15-*trans*-diastereoisomers, which may point in favor of the stereospecificity of the studied reaction. However, since products **3** and **4** were isolated chromatographically in an overall yield of ~57%, and the minor *cis*-diastereoisomers may have been lost in the process of isolation, it is only possible to speak with confidence about the stereoselectivity of the process.

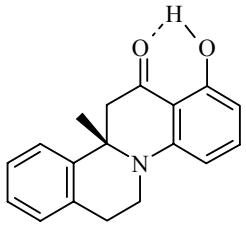
The composition and structure assigned to acetoxy derivatives **3** and **4** are in agreement with the results of elemental analysis and spectral data.

In the mass spectra of acetoxy derivatives **3** and **4** signals were present corresponding to the molecular ions and accompanying them were signals of the $[M+1]^{+\cdot}$ ion-radical, characteristic of nitrogen-containing heterocycles, and also a $[M-15]^{+}$ peak corresponding to the product of ion fragmentation with fission of a methyl group. The fragmentation pathways of the molecular ions of compounds **3** and **4** are therefore different. For the first the most intense (≥40%) were the ion-radicals with masses 264, 253, 238, 210, and 144, and for the second the ion-radicals with masses 324, 280, 264, 236, and 115.

Absorption bands (AB) were present in the IR spectra of acetates **3** and **4** at ~1750 and ~1240 cm^{-1} caused by the vibrations of C=O and C–O–C bonds and confirmed the presence of ester groupings in the structures of these compounds [9]. Intense asymmetric AB were located at 1680-1710 cm^{-1} linked with the

presence of carbonyl groups at positions 12 and 17a [9], and an AB of medium intensity (35-40%) at ~1630 cm^{-1} was assigned to the vibrations of the $C_{(13)}=C_{(14)}$ bond. Differentiation of the spectral contours in the 1670-1715 cm^{-1} region showed that the AB located in this region of the spectrum are composite and are caused by contributions of 4-6 components of different intensity. The two most intense are probably linked with the symmetric and antisymmetric stretching vibrations of the C=O groups, and the components of low intensity with the deformation vibrations of the same groups. However a strict assignment of these AB is still difficult. In the IR spectra AB of medium intensity were also present at 740-790 cm^{-1} characteristic of the vibrations of C–N bonds. Combination of the data considered therefore confirms the presence in the molecules of derivatives **3** and **4** both of acetoxy groups and of the $N_{(8)}–C_{(14)}=C_{(13)}(– C_{(12)}=O)–C_{(17a)}=O$ fragments.

As with the 8-azasteroids described previously, which contain aminovinyldicarbonyl fragments [3, 6, 8, 9], in the electronic absorption spectra of derivatives **3** and **4** two intense (log ε >4) asymmetric AB were present caused by $\pi\rightarrow\pi^*$ electronic transitions. Differentiation of the spectral contours showed that the long wave AB (300-320 nm) have a composite character and are caused by contributions of several components with maxima at 291.8 and 308.8 nm in the case of compound **3** and 291.2, 310, and 324.7 nm in the case of compound **4**. At the same time the short wave AB (260-270 nm) retained their shape after differential treatment procedure enabled their more precise positions to be established as 264.7 for acetate **3** and 262.7 for acetate **4**. The significant difference of the 15-acetoxy derivative **4** from its 17-substituted isomer **3** is the presence in the electronic absorption spectrum of a weak long wave AB at ~380 nm and a yellow-green luminescence of solutions in alcohol. These properties of derivative **4** may be caused by contaminants formed for example as a result of its decomposition to phenol **5**.



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However proof of such a hypothesis has still not been successfully obtained, since acetates **3** and **4** do not survive the conditions of chromato-mass spectrometry, and methods of TLC and NMR are insufficiently sensitive. The differences in the position of the long wave AB of compounds **3** and **4** are extremely eloquent and of principal importance for structural assignments. The indicated AB is located at ~312 nm for the 15-acetoxy derivative **4** and at ~305 nm for the 17-acetoxy derivative **3**. An analogous difference in the position of the long wave AB is also observed in the case of the corresponding 15- and 17-hydroxy derivatives [12].

The ^{1}H NMR method turned out to be most informative when studying the structure of compounds **3** and **4**, and enabled convincing stereostructural assignments to be carried out on the basis of the observed spectral differences (IR, UV, ^{1}H NMR, and mass spectrum). In the ^{1}H NMR spectra of both compounds there were signals for the protons of the isoquinoline (**AB**) and quinolone (**CD**) fragments confirming their common nature with the previously described derivatives of the 8-aza-*D*-homogona-12,17a-dione series [3, 9]. A characteristic of the spectra of derivatives **3** and **4** is the presence of three-proton singlets for the resonance of the 9-Me group and the 15- and 17-acetoxy substituents.

An important difference in the spectra of compounds **3** and **4** is the size of the chemical shift and form of the signal of the methine proton found in the same position as the acetoxy group. In the case of acetate **3** the 15-H signal is found at 5.20 ppm and is a doublet of doublets with coupling constants J_1 = 5.0 and J_2 = 13.0 Hz, indicating its quasiaxial disposition. The 17-H signal of acetate **4** is however found at 6.01 ppm and has the form of a triplet with coupling constant $J_{1,2}$ = 3.0 Hz, indicating its quasiequatorial situation.

The difference in chemical shifts of the 7-H_e protons of compounds **3** and **4** of 0.33 ppm is also important. It is linked with the differences in the stereoelectronic environment of the protons mentioned. In the spectrum of acetate **3** the chemical shift of the 7-H_e proton corresponds to the chemical shift of analogous protons of 15-unsubstituted 8-azasteroids (δ 4.05-4.30 ppm [3, 9]). In the spectrum of acetate **4** the signal of the analogous proton is displaced towards high field by 0.33 ppm, which may be explained by the anisotropic influence of the quasiaxial 15-acetoxy group.

The data of NOE for compound **4** showed the presence of long range spin-spin interactions of the $C_{(7)}H_2$ group protons with the 15-H_e proton both in direct and in reverse experiments. In the case of compound **3** long range spin-spin interactions were observed for the protons of the $C_{(7)}H_2$ and $C_{(15)}H_2$ groups. The long range spin-spin interactions for other groups of protons are shown in the Scheme.

EXPERIMENTAL

The 3,4-dihydroisoquinoline **1** used in the investigation was obtained by the cyclodehydration of homoveratrylacetamide with phosphorus oxychloride according to Bischler–Napieralski [14], and the β,β'-triketone **2** by the known procedure of [15]. A check on the progress of reactions and the homogeneity of products was effected by TLC on silica gel F_{60} 254 plates (Merck), eluent was chloroform–methanol, 9.5:0.5, visualizing in UV light or iodine vapor with subsequent calcining at 250-350°C. Melting points were determined on a Boetius heating block. The IR spectra were obtained on a UR-20 instrument for KBr disks. The UV spectra were taken on a Specord M-400 spectrophotometer for solutions in ethanol. 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 NMR spectra were recorded on a Bruker AC-200 (200 MHz) radiospectrometer, solvent was $CDCl_3$, internal standard TMS, precision of measurement was 0.5 Hz.

***rac*-17-Acetoxy-9-methyl-8-aza-*D*-homogona-1,3,5(10),13-tetraene-12,17a-dione (3) and *rac*-15-Acetoxy-9-methyl-8-aza-*D*-homogona-1,3,5(10),13-tetraene-12,17a-dione (4).** A mixture of isoquinoline **1** (131 mg, 1 mmol) and β,β'-triketone **2** (191 mg, 1 mmol) in ethanol (4 ml) was boiled for 5 h in an atmosphere of argon, following the progress of the reaction by TLC. The reaction mixture was then evaporated, the dry residue washed with ether, dissolved in chloroform, and subjected to flash chromatography on silica gel 5/40μ (Chemapol) (8 g), eluting with chloroform–methanol, 9.5:0.5. According to chromato-mass spectrometry the first eluates contained a mixture of low molecular byproducts (up to 180 mass units), among which 2,6-dihydroxyacetophenone was present (2-acetylresorcinol, $[M]^{+\cdot}$ 152.15). From the second portion of eluate, after evaporation and crystallization of the obtained residue from alcohol–ether, the 15-acetoxy derivative **4** (77 mg, 25%) was obtained (R_f 0.3) as yellow prismatic crystals; mp 235-242°C (decomp.). IR spectrum, ν, cm^{-1}: 2850-3020, 1751, 1680-1710, 1630, 1518-1542, 1500, 1459, 1385, 1360, 1340, 1212-1244, 1146, 1045, 740-780. UV spectrum, λ_{max}, nm (ε): 261.6 (13275), 311.6 (14390), 377.3 (1035); λ_{min} nm (ε): 230.4 (3760), 280.4 (5560), 359.3 (955). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60 (3H, s, 9-CH_3); 2.20 (3H, s, 15-$COCH_3$); 2.04-2.30 (2H, m, 16,16-H_2); 2.30-2.64 (2H, m, 17,17-H_2); 2.68 (1H, d, J = 16.0, 11-H_B); 2.80 (1H, d, J = 16.0, 11-H_A); 2.91 (1H, tt, J = 3.0, J = 3.0, J = 15.0, 6-H_e); 3.13 (1H, dtd, J = 3.0, J = 13.0, J = 15.0, 6-H_a); 3.32 (1H, ddd, J = 3.0, J = 13.0, J = 13.0, 7-H_a); 3.94 (1H, tt, J = 3.0, J = 3.0, J = 13.0, 7-H_e); 6.01 (1H, t, J = 3.0, J = 3.0, 15-H_e); 7.09-7.36 (4H, m, 1-, 2-, 3-, 4-H). Mass spectrum, *m/z* (I_{rel}, %): 340.35 (5.60) $[M+1]^{+\cdot}$; 339.35 (23.65) $[M]^{+\cdot}$; 325.30 (11.04); 324.30 (46.47); 296.30 (13.72); 282.30 (9.67); 281.30 (20.01); 280.30 (83.25); 279.25 (9.63); 278.30 (6.88); 269.25 (8.82); 268.25 (6.00); 266.25 (15.58); 265.25 (20.05); 264.25 (91.89); 262.25 (6.88); 254.25 (35.45); 252.25 (11.54); 249.20 (8.71); 238.25 (7.27); 237.25 (11.46); 236.25 (58.54); 208.25 (16.76); 196.20 (9.42); 194.25 (6.71); 182.20 (7.61); 180.20 (10.26); 168.15 (8.70); 167.15 (10.56); 152.10 (6.40); 146.15 (8.60); 145.15 (8.19); 144.15 (20.18); 143.15 (16.42); 142.15 (6.63); 141.10 (7.21); 132.25 (9.40); 131.20 (10.97); 130.10 (12.81); 129.15 (17.32); 128.10 (33.31); 127.10 (12.87); 118 (7.11); 117.15 (14.00); 116.15 (12.00); 115.10 (40.24); 110.45 (6.18); 108.70 (8.41); 105.05 (10.00); 104.05 (7.88); 103.10

(18.18); 102.10 (12.97); 95.60 (6.43); 90.80 (31.05); 89.10 (9.94); 85 (7.17); 83 (10.32); 79.05 (12.16); 78.05 (10.09); 77.05 (33.83); 76.05 (7.36); 67.05 (7.37); 66.05 (8.55); 65.05 (27.38); 64.05 (7.79); 63.05 (14.72); 60 (18.39); 55.05 (24.00); 53.05 (20.10); 52.05 (9.65); 51.05 (17.58); 45.10 (25.50); 44.10 (16.83); 43.10 (100); 42.10 (13.77); 41.10 (21.17); 39.10 (32.06); 36.05 (7.77). Found, %: C 70.83, 70.72; H 6.22, 6.28; N 4.05, 4.11. $C_{20}H_{21}NO_4$. Calculated, %: C 70.78; H 6.24; N 4.13. M 339.39.

The 17-acetoxy derivative **3** (99 mg, 32%) was isolated from the third portion of eluate in the form of pale-yellow needles (R_f = 0.19); mp 213-216°C (decomp.). IR spectrum, ν, cm^{-1}: 2830-3000, 1753, 1680-1715, 1630, 1530, 1504, 1447-1470, 1420, 1386, 1222-1262, 1141, 1053, 789, 778. UV spectrum, λ_{max}, nm (ε): 265 (15190); 304.6 (16065); λ_{min}, nm (ε): 229.3 (995); 280 (8250). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60 (3H, s, 9-CH_3); 1.94-2.40 (3H, m, 16-H_2, 15-H); 2.18 (3H, s, 17-$COCH_3$); 2.62-2.95 (1H, m, 15-H); 2.64 (1H, d, *J* = 16.0, 11-H_B); 2.77 (1H, d, *J* = 16.0, 11-H_A); 2.95 (1H, tt, *J* = 3.5, *J* = 3.5, *J* = 15.0, 6-H_e); 3.13 (1H, dtd, *J* = 3.5, *J* = 13.0, *J* = 15.0, 6-H_a); 3.42 (1H, ddd, *J* = 3.5, *J* = 13.0, *J* = 13.0, 7-H_a); 4.27 (1H, tt, *J* = 3.5, *J* = 3.5, *J* = 13.0, 7-H_e); 5.20 (1H, dd, *J* = 5.0, *J* = 13.0, 17-H_a); 7.08-7.36 (4H, m, 1-, 2-, 3-, 4-H). Mass spectrum, *m/z* (I_{rel}, %): 340.35 (6.72) $[M+1]^{+\cdot}$; 339.35 (24.31) $[M]^{+\cdot}$; 324.30 (14.15); 296.30 (10.20); 280.30 (12.08); 266.20 (9.31); 265.30 (13.25); 264.25 (68.19); 254.20 (9.04); 253.20 (47.31); 252.25 (8.42); 239.20 (9.45); 238.20 (75.77); 236.25 (8.33); 225.20 (12.60); 224.25 (9.80); 211.25 (9.77); 210.25 (60.40); 208.25 (6.42); 197.25 (22.51); 196.25 (15.33); 182.20 (27.41); 180.20 (6.81); 170.20 (11.19); 168.15 (6.59); 167.15 (9.42); 146.15 (7.74); 145.15 (7.64); 144.15 (47.29); 143.15 (13.12); 141.10 (6.77); 131.15 (6.94); 130.10 (15.15); 129.15 (16.61); 128.10 (28.99); 127.10 (10.11); 117.15 (10.05); 116.15 (8.22); 115.10 (28.89); 103.10 (13.80); 102.15 (6.09); 91.05 (16.87); 79.05 (7.70); 78.10 (6.24); 77.05 (20.48); 67.05 (10.19); 66.05 (6.90); 65.05 (15.95); 63.05 (8.34); 60.00 (12.12); 55.05 (14.14); 54.10 (6.83); 53.05 (27.71); 52.05 (6.98); 51.05 (12.25); 45.10 (16.70); 44.10 (21.38); 43.10 (100); 42.15 (12.57); 41.10 (19.96); 39.10 (20.00). Found, %: C 70.69, 70.81; H 6.20, 6.24; N 4.11, 4.07. $C_{20}H_{21}NO_4$. Calculated, %: C 70.78; H 6.24; N 4.14. M 339.39.

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