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Stereoselectivity of the annelation of 3,4-dihydroisoquinolines by 5-monosubstituted 2-acylcyclohexane-1,3-diones

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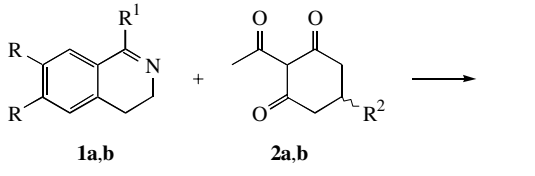
The annelation of 1-methyl-3,4-dihydroisoquinoline by prochiral 5-substituted 2-acylcyclohexane-1,3-diones proceeds diastereoselectively yielding a 9*R*,16*R*:9*S*,16*S* pair of enantiomers rather than a possible mixture of four 8-aza-D-homogona-12,17*a*-dione stereoisomers; this stereoselectivity results from the impossibility of a *threo*-attack on the prochiral , ′-triketone by azomethyne owing to the spatial structure of 2-acylcyclohexane-1,3-dione, on the one hand, and by the steric effect of the C(1) methyl group of 3,4-dihydroisoquinoline, on the other.

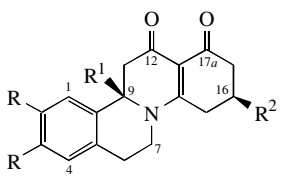
[2+4]-Cyclocondensation of cyclic Schiff bases with -dicarbonyl and , ′-tricarbonyl compounds and their derivatives is widely used for the synthesis of nitrogen-containing heterocycles.[1] In particular, 8-azasteroids with valuable immunological properties have been obtained by this way.[2,3] A considerable disadvantage of 8-aza- and 8-aza-D-homogonanes obtained by this way is their racemic character, which is the main obstacle to their use in medicine and veterinary medicine.

In the cyclocondensation of 3,4-dihydroisoquinoline with 2-acylcycloalkane-1,3-diones, which yields 8-azasteroid ABCD-tetracycles, a C(9) asymmetric centre is formed. It is obvious that the cyclocondensation of azomethynes and , ′-triketones bearing asymmetric centres will give a mixture of stereoisomers at inadequate stereoselectivity. Thus, 16-methylsubstituted[4] and 16-phenylsubstituted[5(a),(b)] 8-aza-D-homogona-12,17*a*-diones have been obtained as a mixture of C(9) and C(16) stereoisomers, which are different to separate by chromatography. One of the two formed 9*R*,16*R*:9*S*,16*S* and 9*R*,16*S*:9*S*,16*R* pairs of enantiomers was predominant (6:4 to 9:1, NMR data). This fact is indicative of the stereoselectivity, but its degree was rather low. It was difficult to attribute a relative configuration to one or another pair of the formed enantiomers on the basis of spectral studies. On the other hand, we found that, in some cases, the introduction of alkyl substituents into the C(1) reaction centre of 3,4-dihydroisoquinoline does not hinder the reaction,[2(a),(b)] but it completely blocks the reaction in other cases.[6] It is evident that the substitution of 3,4-dihydroisoquinolines at the C(1) centre does not influence the reactivity but affects the transition state during the reaction.



1a,**b** **2a**,**b**

a R = H, R^1 = R^2 = Me
b R = OMe, R^1 = Me, R^2 = Ph



3a,**b**

Scheme 1 The relative configuration of C(9) and C(16) centres in compounds **3** corresponds to the 9*S*,16*S*-stereoisomer.

An extremely high degree of regio- and stereoselectivity of this cyclocondensation has been found when unsymmetrical (4-substituted) 2-acetyldimedone derivatives have been used.[7] Thus, it seems to be very important to establish minimum spatial and structural requirements imposed on substrates, which can ensure guaranteed regio- and stereochemical results. This can form a basis for the development of regio- and stereocontrolled synthesis of 8-azasteroids with the required functionality at pharmacologically significant positions of a steroid ABCD-tetracycle and stereochemistry of the C(9) asymmetric centre formed during the reaction.

We have demonstrated that the cyclocondensation of 1-methyl-3,4-dihydroisoquinolines **1a**,**b** with 5-substituted 2-acylcyclohexane-1,3-diones **2a**,**b** bearing a C(5) prochiral centre† resulted in 16-substituted 8-aza-D-homogonane derivatives **3a**,**b**, which are chromatographically uniform (TLC) and spectrally pure.‡ The structure of 9*R*,16*R*:9*S*,16*S* enantiomeric pairs of diastereoisomers with the *cis*-arrangement of C(9) and C(16) substituents has been attributed to the compounds according to spectral studies and X-ray diffraction analysis of compound **3a** (Figure 1, where the 9*S*,16*S* stereoisomer is presented).[8,§]

To explain this stereochemical result, we examined the structure of 3,4-dihydroisoquinolines **1a**,**b** and , ′-triketones **2a**,**b** using Dreiding models. This analysis demonstrated that a dihydropyridine ring in 3,4-dihydroisoquinolines has a distorted sofa conformation. It follows from the NMR data that this ring undergoes fast conformational conversions; thus, resonance signals of the C(3)–C(4) ethylene fragment appear as A_2X_2 degenerated triplets (δ ~ 3.0 and 4.0 ppm, J ~ 7–8 Hz).¶ On this basis we can conclude that the steric structure of a dihydropyridine ring of 3,4-dihydroisoquinolines cannot influence considerably the stereochemical result of the annelation.

† Cyclocondensation has been carried out in ethanol (at room temperature or at boiling) with the use of equimolar amounts of reagents as described for a general method.[7]

‡ For **3a**: colourless small needles, mp 222–224 °C (ethyl acetate–hexane), yield 85%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.14 [d, 3H, C(16)Me, J 6.0 Hz], 1.59 [s, 3H, C(9)Me], 1.86–2.56 [m, 5H, $C(15)H_2$, C(16)H and $C(17)H_2$], 2.26 [d, 1H, $C(11)H_B$, J 15.5 Hz], 2.78 [d, 1H, $C(11)H_A$, J 15.5 Hz], 2.96 [tt, 1H, $C(6)H_e$, J 3.5 and 16.0 Hz], 3.13 [ddd, 1H, $C(6)H_a$, J 3.5, 12.0 and 16.0 Hz], 3.39 [ddd, 1H, $C(7)H_a$, J 3.5, 12.0 and 13.5 Hz], 4.28 [tt, 1H, $C(7)H_e$, J 3.5 and 13.5 Hz], 7.10–7.36 [m, 4H, C(1)H, C(2)H, C(3)H and C(4)H].

For **3b**: colourless small needles, mp 273–275 °C (ethanol–diethyl ether), yield 92%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.61 [s, 3H, C(9)Me], 2.56–2.94 [m, 4H, $C(15)H_2$ and $C(17)H_2$], 2.62 [d, 1H, $C(11)H_B$, J 11.0 Hz], 2.72 [d, 1H, $C(11)H_A$, J 11.0 Hz], 3.02 [m, 1H, $C(16)H_a$], 3.12 [tt, 1H, $C(6)H_e$, J 3.5 and 12.0 Hz], 3.36 [ddd, 1H, $C(6)H_a$, J 3.5, 12.0 and 12.0 Hz], 3.46 [ddd, 1H, $C(7)H_a$, J 3.5, 12.0 and 12.0 Hz], 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.24 [tt, 1H, $C(7)H_e$, J 3.5 and 12.0 Hz], 6.60 [s, 1H, C(4)H], 6.64 [s, 1H, C(1)H], 7.24–7.46 (m, 5H, aromatic).

§ Crystallography for **3a**: $C_{19}H_{21}NO_2$, monoclinic, space group $P2_1/n$, with a = 13.292(2), b = 8.404(1), c = 13.986(2) Å β = 97.170(10)°, V = = 1550.1(4) Å^3, Z = 4, D_{calc} = 1.266 g cm^{-3} and μ = 0.82 cm^{-1}. X-Ray diffraction data were collected at 293 K on a Nicolet R3m diffractometer (MoK radiation) with $\omega/2\theta$ scans, $2 < \theta < 30°$. The structure was solved and refined with the SHELX-97[8] package of crystallographic programs. Refinement was converged with R_1 = 0.0459, wR_2 = 0.1196 [2689 reflections with $I > 2\sigma(I)$] and R_1 = 0.0809, wR_2 = 0.1535 for all data (4539 reflections). Atomic coordinates, bond lengths, bond angles and thermal parameters will be published elsewhere.

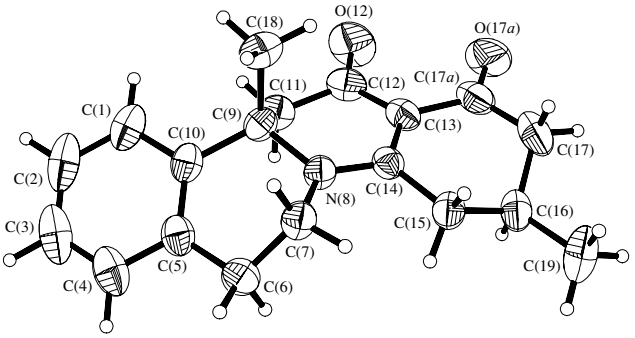
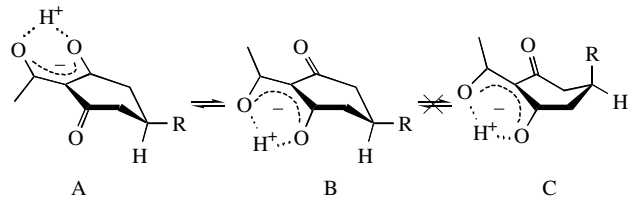


Figure 1 ORTEP-III plot of the 9*S*,16*S* stereoisomer. Ellipsoids correspond to 50% probability.

As for , ′-triketones **2a**,**b**, the Dreiding models demonstrated that a 1,3-dicarbonyl cyclohexane ring is flattened due to the complete enolization of a , ′-tricarbonyl fragment and has a sofa conformation. According to the ^{1}H NMR data, only the conformation with the quasi-equatorial position of a C(5) substituent is realized. This is evident from the A_2B_2X spin–spin interactions observed for C(4) and C(6) methylene and C(5) methyne protons, where the quasi-axial C(5) proton (δ 2.02 ppm, ^1J 4.0 Hz, ^2J 11.0 Hz) acts as an X part, C(4)–H$_e$ and C(6)–H$_e$ protons (δ 2.54 ppm, ^1J 4.0 Hz, ^2J 16.0 Hz) play the role of an A_2 part, and C(4)–H$_a$ and C(6)–H$_a$ protons (δ 2.21 ppm, ^1J 11.0 Hz, ^2J 16.0 Hz) present a B_2 part (Scheme 2).††

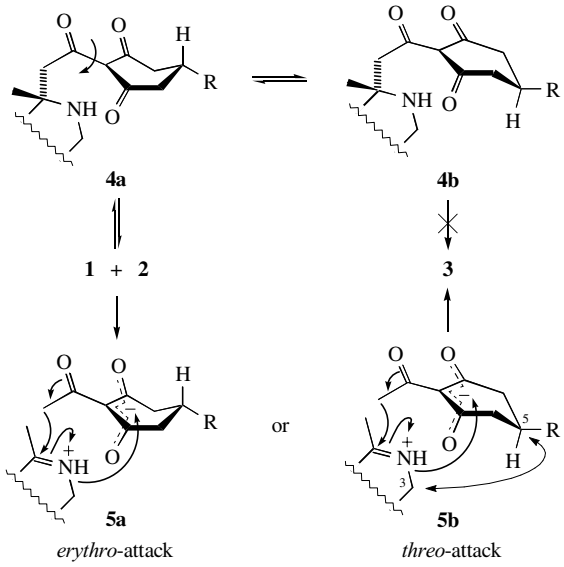
It may be assumed that C(5) quasi-axial conformers of , ′-triketones **2a**,**b** are absent due to stereoelectronic interactions between C(5) substituents (Me, Ph) with the -electron cloud of the enolized , ′-triketone group. Moreover, 2-acetylcyclohexane-1,3-diones **2a**,**b** exist in solutions as equilibrium mixtures of atropomeric keto-enols A and B with a rather rigid sofa conformation of cyclohexane rings, where the C(5) substituent is fixed in a quasi-equatorial position. Conversion of these conformations into the C conformation with a quasi-axial orientation of the C(5) substituent is prohibited. Thus, there is a pronounced difference in possible approaches of azomethyne to a , ′-triketone fragment. Note that, while the keto–enol tautomerism of 2-acylcycloalkane-1,3-diones has been studied in considerable detail,[9] possible conformations of , ′-triketones and their role in the stereochemistry of the 3,4-dihydroisoquinoline annelation were not analysed and discussed earlier.

Cyclocondensations of 3,4-dihydroisoquinolines with 2-acylcycloalkane-1,3-diones have been supposed to proceed through intermediate tricyclic Mannich bases **4a**,**b** which undergo cyclodehydration under the reaction conditions to form tetracyclic 8-azasteroids.[5(a)] However, this suggestion has no experimental justification; moreover, some published experimental data on the cyclocondensation of alkyl-substituted 3,4-dihydroisoquinolines with substituted 2-acylcycloalkane-1,3-diones[2,7] are contradictory to it. Taking into account the structure analysis of tricyclic adducts **4a**,**b** and the geometric requirements imposed on an attack of the tetrahydroisoquinoline NH group on carbonyl groups of a , ′-triketone, it is reasonable to suppose the simultaneous concerted formation of C–C and C–N bonds *via* six-membered transition states **5a**,**b**. Although the appearance of tricyclic adducts **4a**,**b** is not contrary to the known facts,[10(a)–(e)] it is likely that these derivatives are unstable[10(e)] and easily suffer retro-Michael decomposition to initial substances **1** and **2** and hence take no part in the reaction.



Scheme 2

It is obvious that the interaction of a two-membered C=N fragment of 3,4-dihydroisoquinolines **1a**,**b** with four-membered carbon fragment of , ′-triketones **2a**,**b** determines the stereochemical result of reaction. Different steric requirements are imposed by the simultaneous formation of C–C and C–N bonds *via* intermediate **5a** or **5b**. If the cyclocondensation proceeds *via* six-membered transition state **5a**, a mixture of 9*R*,16*R*:9*S*,16*S* stereoisomers can be obtained, while transition state **5b** leads to a mixture of 9*R*,16*S*:9*S*,16*R* stereoisomers. The *cis*-configuration of C(9) and C(16) substituents, found for product **3a**, indicates that the reaction occurs exclusively *via* transition state **5a**, but state **5b** cannot be realized perhaps due to steric hindrances between the C(3) methylene of 3,4-dihydroisoquinolines **1a**,**b** and the C(5) methyne centre of , ′-triketones **2a**,**b** (Scheme 3).



Scheme 3

Thus, in combination with earlier results,[4,5(a),(b),7(a)–(c)] the experimental data demonstrate that minimum requirements for the diastereoselective cyclocondensation are the presence of a C(1) substituent in 3,4-dihydroisoquinolines and a sofa conformation of 2-acylcycloalkane-1,3-diones, which is fixed by one or another way. The enantioselective synthesis of 8-azasteroids with a given configuration of the C(9) chiral centre can be performed by the interaction of an appropriate 3,4-dihydroisoquinoline and a prochiral , ′-triketone under the above conditions. This C(9) configuration is determined by the configuration of a , ′-triketone chiral centre and by the transition state of cyclocondensation.

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References

1 (*a*) A. L. Mikhal'chuk, O. V. Gulyakevich, K. A. Krasnov, V. I. Slesarev and A. A. Akhrem, *Zh. Org. Khim.*, 1993, **29**, 1236 (*Russ. J. Org. Chem.*, 1993, **29**, 1026); (*b*) A. L. Mikhal'chuk, O. V. Gulyakevich, V. P. Peresada, A. M. Likhosherstov and A. A. Akhrem, *Zh. Obshch. Khim.*, 1993, **63**, 701 (*Russ. J. Gen. Chem.*, 1993, **63**, 494); (*c*) M. von Strandtmann, M. P. Cohen and J. Shavel, Jr., *J. Org. Chem.*, 1966, **31**, 797; (*d*) O. V. Gulyakevich and A. L. Mikhal'chuk, *Mendeleev Commun.*, 1997, 72; (*e*) A. L. Mikhal'chuk and O. V. Gulyakevich, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2353 (*Russ. Chem. Bull.*, 1996, **45**, 2235); (*f*) A. L. Mikhal'chuk, O. V. Gulyakevich, V. P. Peresada, A. M. Likhosherstov and A. A. Akhrem, *Dokl. Ross. Akad. Nauk*, 1997, **356**, 769 [*Dokl. Chem.* (*Engl. Transl.*), 1997, **356**, 227].

¶ For **1a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.39 [t, 3H, C(1)Me, *J* 1.2 Hz], 2.70 [t, 2H, C(4)H_2, *J* 7.2 Hz], 3.66 [ddd, 2H, C(3)H_2, *J* 1.2, 7.2 and 7.2 Hz], 7.17 [d, 1H, C(5)H, *J* 7.5 Hz], 7.29 [t, 1H, C(7)H, *J* 7.5 Hz], 7.35 [t, 1H, C(6)H, *J* 7.5 Hz], 7.48 [d, 1H, C(8)H, *J* 7.5 Hz].

†† For **2a**: ^{1}H NMR (200 MHz, [$^2H_5$]pyridine) δ: 0.86 [d, 3H, C(5)Me, *J* 7.0 Hz], 2.02 [m, 1H, C(5)H_a], 2.21 [dd, 2H, C(4)H_a and C(6)H_a, *J* 11.0 and 16.0 Hz], 2.54 [dd, 2H, C(4)H_e and C(6)H_e, *J* 4.0 and 16.0 Hz], 2.63 [s, 3H, C(2)COMe], enolic proton was not detected.

2 (*a*) O. V. Gulyakevich, A. A. Zenyuk, Yu. V. Shklyaev, V. S. Shklyaev and A. A. Akhrem, *Zh. Obshch. Khim*., 1993, **63**, 1891 (*Russ. J. Gen. Chem.*, 1993, **63**, 1319); (*b*) A. L. Mikhal'chuk, O. V. Gulyakevich and A. A. Akhrem, *Khim. Geterotsikl. Soedin*., 1993, 86 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1993, 74]; (*c*) O. V. Gulyakevich, A. L. Mikhal'chuk and A. A. Akhrem, *Khim. Geterotsikl. Soedin*., 1993, 1239 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1993, 1059]; (*d*) O. V. Gulyakevich, A. L. Mikhal'chuk and A. A. Akhrem, *Zh. Obshch. Khim*., 1994, **64**, 1544 (in Russian).

3 (*a*) N. A. Konoplya, O. V. Gulyakevich, A. L. Mikhal'chuk and B. B. Kuzmitsky, *Vesti Akad. Navuk BSSR, Ser. Khim. Navuk*, 1994, 91 (in Russian); (*b*) A. L. Mikhal'chuk, O. V. Gulyakevich and G. S. Lyubin, *Khimiya, farmakologiya i mekhanizm deistviya protivoluchevykh sredstv* (*Chemistry, pharmacology and action mechanism of anti-radiation remedies*), Ministry of Public Health, Institute of Biophysics, Moscow, 1990, p. 47 (in Russian).

4 A. A. Akhrem, F. A. Lakhvich, V. N. Pshenichny, S. U. Sagaydak, O. V. Gulyakevich, B. B. Kuzmitsky, L. P. Malayeva and Yu. L. Zhuravkov, *USSR Patent SU 1039186, Byull. Izobret*., 1993, nos. 41-42 , 201 (*Chem. Abstr.*, 1995, **123**, 306620n).

5 (*a*) A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov and I. L. Rubinova, *Zh. Org. Khim*., 1998, **34**, 956 (*Russ. J. Org. Chem.*, 1998, **34**, 906); (*b*) A. A. Akhrem, A. M. Moiseenkov, V. A. Krivoruchko, F. A. Lakhvich and A. I. Poselenov, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1972, 2078 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1972, **21**, 2014).

6 A. L. Mikhal'chuk, O. V. Gulyakevich, Yu. V. Shklyaev, V. S. Shklyaev and A. A. Akhrem, *Zh. Obshch. Khim*., 1997, **67**, 2062 (in Russian).

7 (*a*) O. V. Gulyakevich, A. L. Mikhal'chuk, A. I. Verenich, D. B. Rubinov, A. A. Zenyuk and A. A. Akhrem, *Enaminy v organicheskom sinteze* (*Enamines in organic synthesis*), Ur. Otd. RAN, Ekaterinburg, 1996, p. 111 (in Russian); (*b*) A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov and A. A. Akhrem, *Khim. Geterotsikl. Soedin*., 1993, 374 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1993, 313].

8 (*a*) G. M. Sheldrick, *Program for Crystal Structure Refinement*, University of Gö tingen, 1997; (*b*) G. M. Sheldrick, *Acta Crystallogr*., 1990, **A46**, 467; (*c*) G. M. Sheldrick, Z. Dauter, K. S. Wilson, H. Hope and L. Sieker, *Acta Crystallogr*., 1993, **D49**, 18.

9 (*a*) V. G. Avakyan, V. V. Gromak and A. E. Yatsenko, *Izv. Akad. Nauk, Ser. Khim*., 1994, 57 (*Russ. Chem. Bull.*, 1994, **43**, 50); (*b*) V. Bertolasi, P. Gilli, V. Feretti and G. Gilli, *J. Chem. Soc., Perkin Trans. 2*, 1997, 945; (*c*) S. Bolvig, F. Dnus and P. E. Hansen, *Magn. Reson. Chem*., 1998, **36**, 315.

10 (*a*) N. S. Kozlov, K. I. Gusak and S. A. Makhnach, *Khim. Geterotsikl. Soedin*., 1996, 960 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1996, 822]; (*b*) N. S. Kozlov, K. I. Gusak and S. A. Makhnach, *Khim. Geterotsikl. Soedin*., 1996, 34 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1996, 30]; (*c*) J. C. Pelletier and M. P. Cava, *Synthesis*, 1987, 474.

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