Direct synthesis of 17a-ethoxyimino-8-aza-D-homogonanes by annelation of 3,4-dihydroisoquinolines with 2-acetyl-5,5-dimethyl-3-ethoxyiminocyclohexanone

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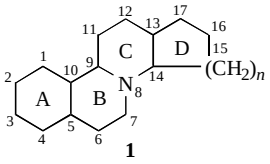
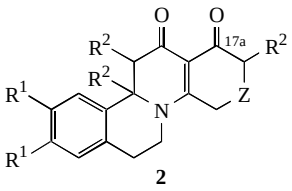
The annelation reaction of Schiff bases by β,β′-tricarbonyl compounds has been extended to 3-ethoxyimino derivatives of 2-acylcyclohexane-1,3-diones. The first direct synthesis of 8-aza-D-homogonanes with a modified carbonyl group at the pharmacologically significant C(17a) position has been carried out.

The 8-aza-steroids (benzo[*a*]cycloalkano[*f*]quinolizines) **1**, being structurally similar to the important bioregulators of both the animal and plant kingdoms, represent a wide class of condensed nitrogen-containing heterocycles, which have both steroid and alkaloid isosteric fragments.[1] These compounds possess valuable biological properties. For example, 8-aza-D-homogona-12,17a-diones **2** act as immunomodulators; moreover, both the degree and the direction of their effect may be modulated by transformations in the CD fragment of the ABCD tetracyclic 8-azasteroidal skeleton.[2] This, unambigously, makes 8-azasteroids very interesting objects as a basis for the development of safe remedies for the correction of human and animal immunity. However, the possibilities for regioselective transformation of the C(12,17a)-β-dicarbonyl group of **2** are very limited,[3] and there are no methods for selective conversion of the C(17a) carbonyl group, for example, into the imino or oxyimino functions.



1

n = 1, 2



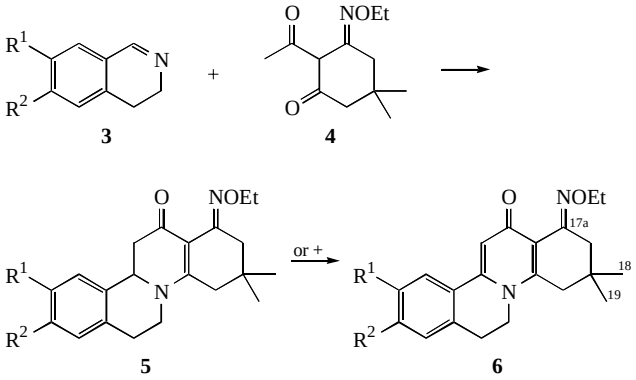
2

R^1 = H, OH, OMe
R^2 = H, alkyl ...
Z = bond, CH_2, CHMe, CMe_2 ...

The annelation of Schiff bases by 2-acetylcycloalkanones,[4] 2-acylcycloalkane-1,3-diones[5] and 2-(1-aminoethylidene)cyclohexane-1,3-diones[6] is well documented. Thus, among several approaches to the (17a)-modified derivatives of **2** the most attractive is the cyclocondensation of 3,4-dihydroisoquinolines **3** with accessible oxyimines **4** (Scheme 1),[7] which contain the β-dicarbonyl fragment necessary for the condensation. Advantageously, and contrary to the unsubstituted oximes of β-di- and β,β′-tricarbonyl compounds, they fail to convert into isoxazoles by means of intramolecular cyclodehydration.[8]

Cyclocondensation of 3,4-dihydroisoquinolines **3a**,**b** with an equimolar quantity of β,β′-oxyiminodiketone **4** has been carried out in boiling methanol or ethanol (inert atmosphere, 11–20 h, TLC control) as described for the general method of annelation for β-di- and β,β′-triketones.[4,5] In contrast to the latter reaction, which yields derivatives of type **2**, annelation of **3a**,**b** with oximine **4** leads to dienones **6a**,**b** (yields 69–71%) or to a mixture of the derivatives **5a**,**b** and **6a**,**b**,† the latter being predominant. If contact with atmospheric and acidic catalysis are avoided, both in the course of the reaction, and during the product isolation, only enones **5a**,**b** are obtained in 83–89% yields.

Studies of the properties of enones **5a**,**b** reveal their sensitivity to an acidic environment and to atmospheric oxygen, as well as their thermal lability. Keeping the sample of **5a** in a solution containing catalytic quantities of *p*-toluenesulfonic acid in air, and filtration of the solution of **5b** through acidic silica gel, as well as raising the temperature of the reaction (boiling in isopropanol or butanol), afforded the corresponding



3 **4**

5 **6**

a $R^1 = R^2$ = OMe
b R^1 = H, R^2 = OMe

Scheme 1

dienones **6**. Thus, the derivatives **6** are the products of dehydration of the initially formed enones **5**. It is noteworthy that there are no molecular peaks in the mass spectra of **5**, so they are identical with those of **6**. This indicates the lability of

† Satisfactory elemental analyses, as well as IR, UV, ^{1}H and ^{13}C NMR spectra, were obtained for all new compounds.

For **5a**: mp 167–171 °C (decomp.); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.04 [s, 3H, C(16)–Me], 1.10 [s, 3H, C(16)–Me], 1.30 (t, 3H, $NOCH_2$*Me*, *J* 7.0 Hz), 2.31 [d, 1H, C(17)H_B, *J* 16.5 Hz], 2.40 [d, 1H, C(15)H_B, *J* 16.0 Hz], 2.43 [d, 1H, C(17)H_A, *J* 16.5 Hz], 2.60 [t, 1H, C(11)H_B, *J* 15.5 Hz], 2.64 [d, 1H, C(15)H_B, *J* 16.0 Hz], 2.78 [tt, 1H, C(6)H_e, *J* 15.0, 4.0, 4.0 Hz], 2.87 [dd, 1H, C(11)H_A, *J* 15.5, 4.0 Hz], 3.02 [m, 1H, C(6)H_a, *J* 15.0, 12.0, 4.0 Hz], 3.22 [ddd, 1H, C(7)H_e, *J* 12.0, 12.0, 4.0 Hz], 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.14 [tt, 1H, C(7)H_a, *J* 12.0, 4.0, 4.0 Hz], 4.23 (q, 2H, $NOCH_2$Me, *J* 7.0 Hz), 4.70 [dd, 1H, C(9)H_X, *J* 15.5, 4.0 Hz], 6.60 [s, 1H, C(4)H], 6.66 [s, 1H, C(1)H]; ^{13}C NMR (90 MHz, $CDCl_3$) δ: 14.79 (q, $NOCH_2$*Me*), 28.04 [q, C(18)], 29.36 [s, C(16)], 29.60 [q, C(19)], 29.76 (t), 36.14 (t), 41.53 (t), 43.96 (t), 47.09 (t), 55.97 (q, OMe), 56.03 (q, OMe), 56.91 [d, C(9)], 69.10 (t, $NOCH_2$Me), 104.66 [s, C(13)], 108.39 (d), 110.96 (d), 125.61 (s), 126.13 (s), 148.08 (s), 148.35 (s), 151.99 (s), 163.06 (s), 187.47 (s). IR (KBr, ν/cm^{-1}): 3000–2830, 1645, 1522, 1466–1447, 1357, 1330, 1275, 1222, 1205, 1130, 1062, 866; UV (MeOH) λ_{max}/nm (ε): 201 (41.770), 234 (10.485), 275 (13.685), 339 (9.190), λ_{min}/(ε): 219 (8.005), 248 (7.035), 302 (3.940).

For **6a**: mp 87–92 °C (decomp.); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.07 [s, 6H, MeC(16)Me], 1.31 (t, 3H, $NOCH_2$*Me*, *J* 7.0 Hz), 2.62 [s, 2H, C(17)H_2], 2.64 [s, 2H, C(15)H_2], 3.02 [t, 2H, C(6)H_2, *J* 6.0 Hz], 3.94 [s, 6H, C(2)OMe, C(3)OMe], 4.08 [t, 2H, C(7)H_2, *J* 6.0 Hz], 4.32 (q, 2H, $NOCH_2$Me, *J* 7.0 Hz), 6.74 [s, 1H, C(11)H], 6.95 [s, 1H, C(4)H], 7.18 [s, 1H, C(1)H]; ^{13}C NMR (90 MHz, $CDCl_3$) δ: 14.73 (q, $NOCH_2$*Me*), 27.84 (t), 28.87 [q, C(18), C(19)], 29.99 [s, C(16)], 35.94 (t), 41.49 (t), 44.82 (t), 58.09 (q, OMe), 58.22 (q, OMe), 69.65 (t, $NOCH_2$Me), 108.38 (d), 109.87 (d), 113.626 (d), 118.27 (s), 121.00 (s), 127.48 (s), 144.15 (s), 148.80 (s), 149.75 (s), 151.23 (s), 151.76 (s) , 175.08 [s, C(12)]. IR (KBr, ν/cm^{-1}): 3000–2830, 1639, 1618, 1525 (sh), 1515, 1475, 1362, 1275, 1218, 1159, 1066, 876; UV (MeOH), λ_{max}/nm (ε): 232 (21.240), 275 (21.040), 324 (13.700), λ_{min}/nm (ε): 218 (19.125), 260 (15.745), 302 (11.255).

For **5b**: mp 110–113 °C (decomp.).

For **6b**: mp 95–100 °C (decomp.).

these compounds under the conditions of mass spectral analysis. In order to obtain the derivatives **5** it was necessary to use an inert reaction atmosphere and to avoid acidic catalysis in all stages during the synthesis and isolation.

Thus, the present work has demonstrated the possibility of annelation of the 2-acylcyclohexane-1,3-diones with a modified ring carbonyl group with Schiff bases. This provides a simple, one-step synthesis of 8-azasteroid derivatives with a modified carbonyl group at the pharmacologically significant C(17a) position.

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