An AB + D → ABCD approach to the construction of the 8-azasteroid skeleton by [3+3] cyclocondensation of 3,4-dihydroisoquinolines with ethyl 2-oxocyclopentanecarboxylate as a new annelation reaction for a series of cyclic Schiff's bases

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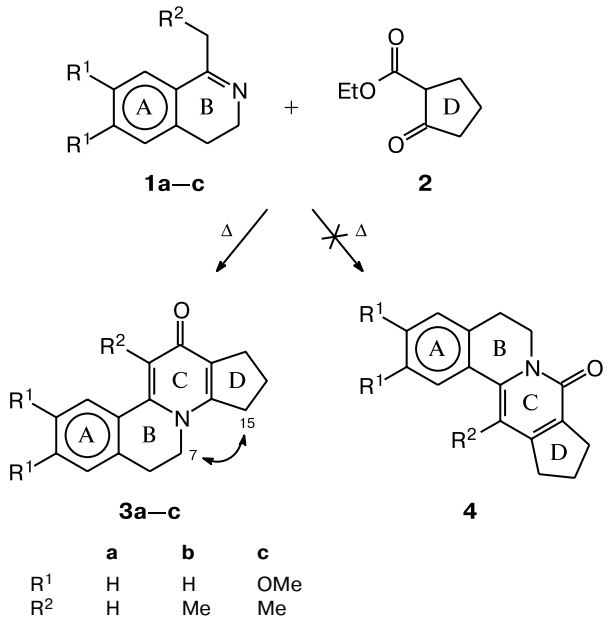
A new approach (AB + D → ABCD) to the construction of tetracyclic 8-azagonane (cyclopenta[5,6]pyrido[2,1-*a*]isoquinoline or benzo[*a*]cyclopenta[*f*]quinolizine) structures was developed and exemplified by cyclocondensation of 1-alkyl-3,4-dihydroisoquinolines with ethyl 2-oxocyclopentanecarboxylate.

Key words: cyclic Schiff's bases, azomethines, enamines, 1-alkyl-3,4-dihydroisoquinolines, β-oxo esters, ethyl 2-oxocyclopentanecarboxylate, cyclopenta[5,6]pyrido[2,1-*a*]isoquinolines, benzo[*a*]cyclopenta[*f*]quinolizines, 8-azagonanes, 8-azasteroids, annelation, [3+3] cyclocondensation.

Annelation of cyclic Schiff's bases with alicyclic and heterocyclic β-di- and β,β´-tricarbonyl compounds or their enol derivatives is used in the synthesis of fused nitrogen-containing heterocycles, which are related to alkaloids or belong to heterocyclic analogs of steroids.[1—7] Annelation of cyclic Schiff's bases or azomethines can be carried out with the use of two approaches involving [2+4] and [3+3] cyclocondensation reactions. [2+4] Cyclocondensation of 3,4-dihydroisoquinolines with β-dicarbonyl compounds, which has been described for the first time in the study,[1] has gained wide acceptance and is used in the synthesis of heterocyclic analogs of steroids.[2,3] [3+3] Cyclocondensation of azomethines with enaminones and enaminodiones, which is based on reactions of 1,3-dinucleophiles (azomethines as the enamine tautomers) with 1,3-dielectrophiles (β-dicarbonyl compounds), has found use relatively recently[4,5] and is not sufficiently developed. Studies devoted to the synthesis of fused nitrogen-containing heterocycles by [3+3] cyclocondensation of azomethines with 1,3-dielectrophiles are few in number.[4—7]

In continuation of studies on the synthesis of fused nitrogen-containing heterocycles, which are related to isoquinoline alkaloids[5,8] or belong to heterocyclic analogs of steroids,[2—4,9—11] we discovered a new annelation reaction of cyclic Schiff's bases, which involves [3+3] cyclocondensation of 1-alkyl-3,4-dihydroisoquinolines (**1a—c**) with ethyl 2-oxocyclopentanecarboxylate (**2**) to give 8-azagonanes, *viz.*, cyclopenta[5,6]pyrido[2,1-*a*]isoquinolines (**3a—c**), (Scheme 1). This reaction provides a new example of [3+3] cyclocondensation of cyclic Schiff's bases or azomethines (3,4-dihydroisoquinolines) with β-dicarbonyl compounds (2-oxocyclopentanecarboxylates) and offers possibilities of synthesizing various heterocycles with the nitrogen atom at the position of fusion starting from readily available cyclic

Scheme 1



	a	b	c
R^1	H	H	OMe
R^2	H	Me	Me

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Schiff's bases, for example, from 1-alkyl-3,4-dihydro-β-carbolines, and β-oxo esters.

We did not observe the formation of isomeric derivatives of cyclopenta[4,5]pyrido[2,1-*a*]isoquinolines (**4**) related to berbane alkaloids,[12] which is indicative of the selectivity of the new reaction.

The structures of 8-azagonanes **3a—c** were confirmed by physicochemical studies. The results of these studies are consistent with the physicochemical characteristics of the related compounds, which have been synthesized earlier by multistep chemical transformations.[13,14] The structures of compounds **3a—c** were conclusively established by nuclear Overhauser enhancement experiments,[15] which revealed the presence of long-range interactions of the $C(7)H_2$ and $C(15)H_2$ protons. As can be seen from comparison of isomeric structures **3** and **4**, these interactions can occur in the case of the spatially close (≈2.5 Å) protons of the CH_2 groups in 8-azagonanes **3** and are highly improbable for the spatially remote protons (≈6 Å) in cyclopenta[4,5]pyrido[2,1-*a*]isoquinolines **4**.

Compounds **3** are of interest as intermediates for the synthesis of benzo[*a*]- and benzo[*a*]cycloalka[*f*]quinolizine derivatives (protoalkaloids and heterocyclic analogs of steroids), which are difficult to prepare with the use of known procedures, as potential biologically active compounds, and also as model compounds for studying the structure—biological activity relationship in a series of fused quinolizine derivatives.[16,17]

To summarize, annelation of cyclic Schiff's bases with β-oxo esters, which was exemplified by cyclocondensation of 3,4-dihydroisoquinolines **1a—c** with ethyl 2-oxocyclopentanecarboxylate (**2**), provides a new one-pot approach (AB + D → ABCD) to 8-azasteroids. These compounds are of interest as immunomodulators.[16,17]

Experimental

The course of the reactions and the purities of the products were monitored by TLC on Silufol UV-254 plates or Silica gel Woelm (fixed layer) using a chloroform—methanol system (9 : 1); visualization was carried out with UV light or iodine vapor followed by heating at 250—350 °C. The melting points were determined on a Boetius hot-stage apparatus. The UV spectra were recorded on a Specord M-400 spectrophotometer. The IR spectra were measured on a UR-20 instrument. The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ with Me_4Si as the internal standard. The mass spectra were obtained on an HP 5890/5972 GC/MS spectrometer equipped with an HP 5MS quartz capillary column (30 m×0.25 mm×0.25 μm); the energy of ionizing electrons was 70 eV.

3,4-Dihydroisoquinolines **1a—c** were prepared under conditions of the Bischler—Napieralski reaction[18] by cyclodehydration of the corresponding phenethylamides with polyphosphoric acid (azomethines **1a,b**) and $POCl_3$ (azomethine **1c**). β-Oxo ester **2** was synthesized by the Dieckmann condensation according to a known procedure.[19]

8-Azagona-1,3,5(10),9(11),13-pentaen-12-one (3a). A mixture of 3,4-dihydroisoquinoline **3a** (1.1 g, 7.5 mmol) and β-oxo ester **2** (2 mL, 13.8 mmol) was heated under argon at 120—160 °C for 7 h and then concentrated. The residue was dissolved in chloroform and chromatographed[20] on silica gel (5 μm, Chemapol; 10 g) using a chloroform—methanol mixture (9 : 1) as the eluent. The eluate was concentrated and the residue was recrystallized from ethanol. 8-Azagonane **3a** was prepared as white needle-like crystals in a yield of 1.3 g (73%), m.p. 235.5—236.5 °C (with decomp.; at 225—230 °C needle-like crystals were transformed into prism-like crystals). Found (%): C, 80.89; H, 6.43; N, 5.77. $C_{16}H_{15}NO$. Calculated (%): C, 80.98; H, 6.37; N, 5.90. M 237.30. MS, *m/z* (I_{rel} (%)): 238 $[M + 1]^{+\bullet}$ (10.5), 237 $[M]^{+\bullet}$ (66.5), 236 $[M - 1]^+$ (100), 222 (3.0), 221 (5.5), 209 (16), 208 (25.5), 207 (7), 192 (6.5), 128 (6), 115 (8.5), 104.5 (7), 103.5 (5), 102 (5.5), 90.5 (5.5), 77 (5). UV, λ_{max}/nm (ε): 215 (16680), 243.8 (18370), 300 (13435); λ_{min}/nm (ε): 226.5 (8255), 258 (3830). IR (KBr), ν/cm^{-1}: 3100—2830, 1622, 1600, 1574, 1555, 1534, 1496, 1460, 1442, 1354, 1263, 1207, 1185, 904, 781. ^{1}H NMR, δ: 2.15 (quint, 2 H, $C(16)H_2$, J = 8.0 Hz); 2.94 (t, 2 H, $C(17)H_2$, J = 8.0 Hz); 3.04 (t, 2 H, $C(15)H_2$, J = 8.0 Hz); 3.08 (t, 2 H, $C(6)H_2$, J = 6.5 Hz); 4.01 (t, 2 H, $C(7)H_2$, J = 6.5 Hz); 6.88 (s, 1 H, C(11)H); 7.26 (m, 1 H, C(4)H); 7.38 (m, 2 H, C(2)H, C(3)H); 7.75 (m, 1 H, C(1)H).

11-Methyl-8-azagona-1,3,5(10),9(11),13-pentaen-12-one (3b). Analogously, heating of a mixture of 3,4-dihydroisoquinoline **1b** (1.2 g, 7.5 mmol) and β-oxo ester **2** (1.2 mL, 8.3 mmol) at 140—160 °C (1.5 h) followed by chromatography and crystallization afforded 8-azagonane **3b** in a yield of 1.2 g (64%) as pale-cream platelet-like crystals, m.p. 187.5—190 °C (from a chloroform—diisopropyl ether mixture, with decomp.). Found (%): C, 81.11; H, 6.89; N, 5.39. $C_{17}H_{17}NO$. Calculated (%): C, 81.24; H, 6.82; N, 5.57. M 251.33. MS, *m/z* (I_{rel} (%)): 252 $[M + 1]^{+\bullet}$ (5.0), 251 $[M]^{+\bullet}$ (35.5), 250 $[M - 1]^+$ (100), 248 (5.5), 111.5 (5.5). UV, λ_{max}/nm (ε): 207.7 (10890), 254.7 (14800), 290.5 (6425); λ_{min}/nm (ε): 229.4 (4610), 265.6 (4745). IR (KBr), ν/cm^{-1}: 3100—2830, 1625—1605, 1600, 1575—1540, 1505—1485, 1460, 1432, 1370, 1260, 948, 770, 752. ^{1}H NMR, δ: 2.15 (t, quint, 2 H, $C(16)H_2$, J = 7.5 Hz); 2.40 (s, 3 H, C(11)Me); 2.98 (t, 2 H, $C(17)H_2$, J = 7.5 Hz); 3.01 (t, 2 H, $C(6)H_2$, J = 6.0 Hz); 3.04 (t, 2 H, $C(15)H_2$, J = 7.5 Hz); 3.94 (t, 2 H, $C(7)H_2$, J = 6.0 Hz); 7.25—7.42 (m, 3 H, C(2)H, C(3)H, C(4)H); 7.70 (m, 1 H, C(1)H).

2,3-Dimethoxy-11-methyl-8-azagona-1,3,5(10),9(11),13-pentaen-12-one (3c). A mixture of 3,4-dihydroisoquinoline **1c** (1.1 g, 5 mmol) and β-oxo ester **2** (1 mL, 6.9 mmol) was heated under argon at 140—180 °C for 7 h. In the course of the reaction, a crystalline compound (**A**) precipitated. After completion of the reaction, compound **A** was filtered off, washed with methanol, and dried. The filtrate and washings were combined. The resulting solution was concentrated to dryness, the residue was subjected to flash chromatography, and the eluate was concentrated. The residue was combined with compound **A** and recrystallized from ethanol. 8-Azagonane **3c** was prepared as white prism-like crystals in a yield of 1.2 g (77%), m.p. 245—248 °C (with decomp.). Found (%): C 73.12, H 6.92; N, 4.43. $C_{19}H_{21}NO_3$. Calculated (%): C, 73.29; H, 6.80; N, 4.50.

M 311.38. MS, m/z (I_{rel} %): 312 $[M + 1]^{+\bullet}$ (12), 311 $[M]^{+\bullet}$ (63), 310 $[M - 1]^{+}$ (100), 297 (8.5), 296 (42.5), 295 (6), 294 (18.5), 280 (8.5), 268 (22), 266 (14.5), 265 (16.5), 252 (9), 237 (7), 236 (12), 225 (11.5), 224 (14.5), 210 (5), 208 (6), 207 (9), 197 (5.5), 196 (8), 141.5 (33), 140 (5.5), 128 (5.5), 126.5 (16.5), 118.5 (5.5), 115 (9), 111.5 (5.5), 103 (5), 102 (5.5), 98.5 (6), 83.5 (5), 77 (6.5), 65 (7). UV, λ_{max}/nm (ε): 216.2 (27600), 241.1 (37565), 260.7 (33970), 310.4 (26890); λ_{min}/nm (ε): 225.7 (26185), 250 (29015), 272.5 (15570). IR (KBr), ν/cm^{-1}: 3100—2830, 1618, 1604, 1557, 1503, 1461, 1340, 1290, 1280, 1261, 1222, 1141, 1083, 1038, 1023, 770. ^{1}H NMR (CF_3COOH—$CDCl_3$), δ: 2.28 (quint, 2 H, C(16)H_2, J = 8.0 Hz); 2.50 (s, 3 H, C(11)Me); 3.04 (t, 2 H, C(6)H_2, J = 6.5 Hz); 3.22 (t, 2 H, C(17)H_2, J = 8.0 Hz); 3.24 (t, 2 H, C(15)H_2, J = 8.0 Hz); 3.92 and 3.98 (both s, 3 H each, OMe); 4.20 (t, 2 H, C(7)H_2, J = 6.5 Hz); 6.87 (s, 1 H, C(4)H); 7.16 (s, 1 H, C(1)H).

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