The annelation of 3,4-dihydroisoquinoline by 2-acetylcycloheptane-1,3-dione: the effect of 2-acylcycloalkane-1,3-dione ring size on the annelation of cyclic Schiff bases

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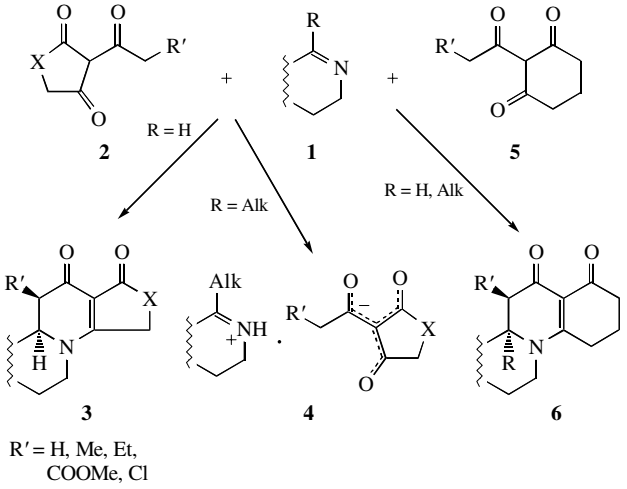
New condensed 3,4-dihydroisoquinoline derivatives — 10,11-dimethoxy-1,2,3,4,5,7,8,12*b*,13,14-decahydrocyclohepta[5,6]pyrido-[2,1-*a*]isoquinoline-1,14-dione [or 2,3-dimethoxy-8-aza-D-dihomogona-1,3,5(10),13-tetraene-12,17*b*-dione] and 2,3-dimethoxy-5,6,8,9,10,11,12,13,14,15,16,16*a*-dodecahydroazacycloundeca[2,1-*a*]isoquinoline-8,13,15-trione — have been obtained by the heteroannelation of 3,4-dihydroisoquinoline by 2-acetylcycloheptane-1,3-dione.

The reactions of cyclic Schiff base annelation (heterocyclization, cyclocondensation) by β-dicarbonyl and β,β′-tricarbonyl compounds or their enol derivatives are useful for the synthesis of condensed nitrogen-containing heterocycles with an angular nitrogen atom and are widely investigated in the last decades.[1] These reactions have been extended to various cyclic and non-cyclic Schiff bases,[1–4] β-dicarbonyl[4–6] and β,β′-tricarbonyl[1,7] compounds and their enol derivatives.[8]

The study of the applicability of 3,4-dihydroisoquinoline annelation by β,β′-tricarbonyl compounds has shown that the interaction between Schiff bases of the aldimine type (**1**, R = H) and 2-acylcyclopentane-1,3-diones (**2**, X = CH_2) or 3-acylthiotetronic acids (**2**, X = S) gives rise to cyclocondensation products **3**.[1,7] When Schiff bases of the ketimine type (**1**, R = Alk) and β,β′-tricarbonyl compounds with five-membered rings **2** have been used, the reaction comes to a stop at the formation of salt **4**.[7,9] When β,β′-tricarbonyl compounds with six-membered rings **5** act as annelation agents, the reaction results in the formation of [2 + 4]cyclocondensation products **6** regardless of substitution at the azomethine carbon atoms of Schiff bases.

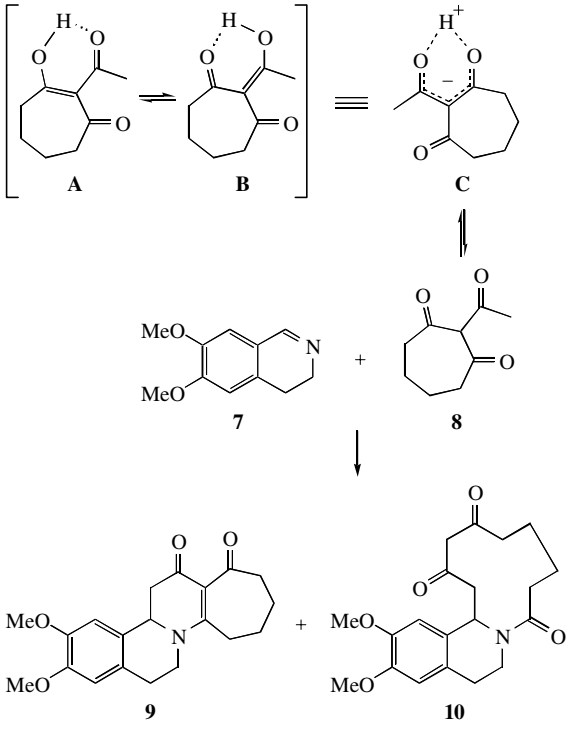


Scheme 1

In order to evaluate the influence of the ring size of 2-acylcycloalkane-1,3-diones on the considered reaction, we have studied the interaction of 3,4-dihydroisoquinoline **7** with 2-acetylcycloheptane-1,3-dione **8**.†

β,β′-Triketone **8**, as well as all β,β′-tricarbonyl compounds with five-membered carbocyclic and heterocyclic rings **2** or six-membered rings **5**, is fully enolised in solutions[12] and exists in the enol–enol (1,5-O,O′-prototrope) tautomeric equilibrium **A** ⇌ **B**, which is a part of the general tautomeric equilibrium involving the β′-carbonyl group into a prototrope process.[1,9] Bearing in mind an extremely high downfield shift of the signal due to the enol proton (δ_{OH} 17.96, $CDCl_3$–TMS) and the impossibility of experimentally detecting enols **A** and **B**, triketone **8** can be represented by quasiaromatic betaine **C** with a chelating proton. Because triketone **8** exhibits physical and chemical characteristics similar to those of β,β′-tricarbonyl compounds **2**, **5**, it can be expected that the interaction of **8** with azomethine **7** yields [2 + 4]cyclocondensation product **9**. In fact, this reaction‡ afforded, along with expected product **9**,§ a substance identified as azacycloundeca[2,1-*a*]isoquinoline **10**.¶ The reliability of the structure of **10** has been confirmed by X-ray diffraction analysis,†† which also revealed that the β-dicarbonyl fragment of **10** is not enolised in crystals (Figure 1) and solutions (^{1}H NMR data).

According to TLC data, tricyclic derivative **10** (R_f = 0.47) was initially formed. Then, product **9** (R_f = 0.28) was formed



Scheme 2

† *2-Acetylcycloheptane-1,3-dione* **8**[10] has been prepared from cycloheptane-1,3-dione according to the known method[11] by O-acetylation followed by O–C-isomerisation by heating in toluene (4 h) in the presence of an equimolar amount of 4-dimethylaminopyridine. Yield of triketone **8** was 55%, bp 85–87 (1 torr). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ: 1.82–1.94 [m, 4H, C(O)CH_2CH_2CH_2CH_2], 2.40 (s, 3H, Me), 2.58–2.78 [m, 4H, C(O)CH_2CH_2CH_2CH_2], 17.96 (s, 1H, OH). IR (film, ν/cm^{-1}): 1660, 1610, 1570. Found (%): C, 64.67; H, 7.12. Calc. for $C_9H_{12}O_3$ (%): C, 64.27; H, 7.19.

and accumulated. When reaction was completed, the ratio of products **9**:**10** was ~3:1. It is noteworthy that the refluxing of the reaction mixture after the consumption of initial reactants **8** and **7** leaded to a gradual decrease in the amount of compound **10** to its complete disappearance. All of these facts allowed us to assume that product **10** can be an intermediate in either the equilibrium reaction between substrates **7** and **8** or the conversion of substrates **7**, **8** into product **9**. The former suggestion was supported by TLC data for a molten sample of **10**, which revealed the presence of substances **7**, **8**, **10** rather than **9**.

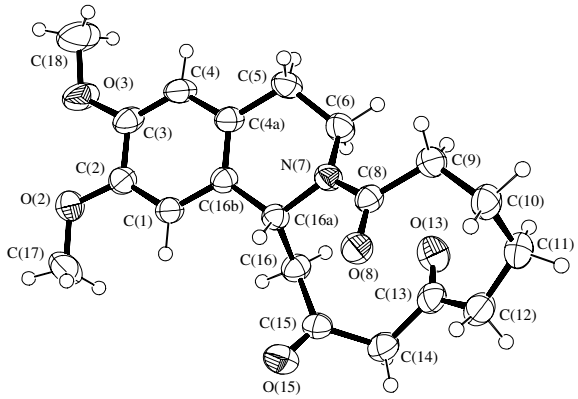


Figure 1 ORTEP III[13(c)] drawing of the molecular structure of **10**. Displacement ellipsoids are shown at the 50% probability level, and hydrogen atoms are represented by spheres of arbitrary radii.

The formation of macrocyclic products like **10** was observed previously in reactions of cyclic Schiff bases with β-dicarbonyl and β,β′-tricarbonyl compounds having a quartenary α-carbon atom.[14] Thus, we can conclude that an increase in the ring size of 2-acylcycloalkane-1,3-dione has an effect similar to that of a quartenary α-carbon atom of β-dicarbonyl and β,β′-tricarbonyl compounds. Taking into account the formation and yield (higher than 20% under non-optimised conditions) of macrocycle **10**, the reaction can be considered as preparative.

Thus, the data on the annelation reactions of Schiff bases by β,β′-tricarbonyl compounds are indicative of an important role of the triketone ring size in the reaction. On the other hand, all available data also suggest that it is impossible to prepare tetracyclic derivatives like **3**, **6** and **9** with a less than five-membered ring D by this method, and it is difficult to predict the results of this reaction extending to β,β′-tricarbonyl compounds with more than seven-membered rings.

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‡ An equimolar mixture of 6,7-dimethoxy-3,4-dihydroisoquinoline **7** and β,β′-triketone **8** was refluxed in methanol or ethanol in an argon atmosphere (TLC: Silica gel 60 F_{254}; chloroform–methanol, 9:1; visualisation in UV light or by iodine vapour followed by burning out at 250–300 °C). After the end of the reaction (the absence of substrates **7** and **8** in the medium), the reaction mixture was evaporated by half and kept in cold. Precipitated **10** was separated by filtration and recrystallised from methanol. The mother liquor was diluted with diethyl ether and kept in cold. Precipitated **9** was recrystallised from ethanol by adding diethyl ether. The combined mother liquors were evaporated, and the residue was chromatographed on SiO_2 with a chloroform–methanol (9:1) eluent. Additional quantities of chromatographically homogeneous products **9** and **10** were isolated from the eluates. The total yield of 10,11-dimethoxy-1,2,3,4,5,7,8,12*b*,13,14-decahydrocyclohepta[5,6]pyrido[2,1-*a*]isoquinoline-1,14-dione [or 2,3-dimethoxy-8-aza-D-dihomogona-1,3,5(10),13-tetraene-12,17*b*-dione] **9** was 70.7%, and that of 2,3-dimethoxy-5,6,8,9,10,11,12,13,14,15,16,16*a*-dodecahydroazacycloundeca[2,1-*a*]isoquinoline-8,13,15-trione **10** was 22%.

§ For **9**: pinkish needles from ethanol–diethyl ether, mp 238.5–239 °C. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ: 1.84 [m, 4H, C(16)H_2, C(17)H_2], 2.28–2.76 [m, 4H, C(15)H_2, C(17a)H_2], 2.56 [t, 1H, C(11)$H_{a(B)}$, *J* 15.5 Hz], 2.79 [dd, 1H, C(11)$H_{e(A)}$, *J* 4.0, 15.5 Hz], 2.86 [tt, 1H, C(6)H_e, *J* 3.0, 12.5 Hz], 3.06 [ddd, 1H, C(6)H_a, *J* 12.5, 12.5, 3.0 Hz], 3.35 [ddd, 1H, C(7)H_a, *J* 3.0, 12.5, 12.5 Hz], 3.84 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.26 [tt, 1H, C(7)H_e, *J* 3.0, 3.0, 12.5 Hz], 4.84 [dd, 1H, C(9)$H_{a(X)}$, *J* 4.0, 15.5 Hz], 6.62 [s, 1H, C(4)H], 6.68 [s, 1H, C(1)H]. ^{13}C NMR (90.53 MHz, $CDCl_3$, TMS) δ: 20.856 (CH_2), 22.157 (CH_2), 28.535 (CH_2), 29.599 (CH_2), 41.237 (CH_2), 44.246 (CH_2), 45.051 (CH_2), 56.044 (2OMe), 57.565 [C(9)], 108.480 [C(4)], 111.042 [C(1)], 113.101 [C(13)], 125.458 [C(10)], 126.110 [C(5)], 148.293 [C(2)], 148.534 [C(3)], 167.196 [C(14)], 187.425 [C(12)], 201.843 [C(17b)]. IR (KBr, ν/cm^{-1}): 3000–2830, 1690, 1622, 1555–1520, 1475–1450, 1343, 1320, 1268, 1238, 1220–1200, 1130, 1000, 848, 778. UV (EtOH) λ_{max}/nm (lg ε): 282.3 (4.05), 318.9 (4.18); λ_{min}/nm (lg ε): 250.0 (3.43). MS, *m*/*z*: 341 [M$^+$]. Found (%): C, 70.31; H, 6.72; N, 4.04. Calc. for $C_{20}H_{23}NO_4$ (%): C, 70.36; H, 6.79; N, 4.10.

¶ For **10**: colourless prisms from methanol, mp 184.5–186 °C. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ: 1.62 [m, 1H, C(10)H], 1.76 [m, 1H, C(11)H], 2.00 [m, 2H, C(10)H, C(11)H], 2.20 [dd, 1H, C(9)H_a, *J* 10.0, 16.0 Hz], 2.34 [dd, 1H, C(12)H, *J* 10.0, 19.0 Hz], 2.60 [dd, 1H, C(9)H, *J* 10.0, 16.0 Hz], 2.80 [m, 2H, C(5)H_a, C(5)H_e], 3.08 [dd, 1H, C(12)H, *J* 10.0, 19.0 Hz], 3.34 [d, 1H, C(14)H_B, *J* 11.0 Hz], 3.35 [dd, 1H, C(16)H_B, *J* 10.0, 16.0 Hz], 3.48 [m, 1H, C(16)H_A], 3.48 [dd, 1H, C(16)H_A, *J* 1.5, 16.0 Hz], 3.78 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.92 [dtd, 1H, C(6)H_a, *J* 3.0, 9.0, 15.0 Hz], 5.77 [dd, 1H, C(16)$H_{a(X)}$, *J* 1.5, 10.0 Hz], 6.56 [s, 1H, C(4)H], 6.72 [s, 1H, C(1)H]. ^{13}C NMR (90.53 MHz, $CDCl_3$, TMS) δ: 22.306 (CH_2), 23.459 (CH_2), 28.779 (CH_2), 32.659 (CH_2), 39.932 (CH), 43.634 (CH), 47.722 (CH), 51.438 [C(16)H_a], 55.938 (OMe), 56.167 (OMe), 60.932 [C(14)], 110.013, 110.672, 125.636, 128.200, 148.007 [C(3)], 148.174 [C(2)], 173.146 [C(8)], 199.888 (CO), 202.576 (CO). IR (KBr, ν/cm^{-1}): 3050–2830, 1709, 1634, 1533, 1470 (sh.), 1451, 1435 (sh.), 1412, 1370, 1345, 1289, 1275–1250, 1231, 1219, 1140–1125, 1035, 862. UV (EtOH) λ_{max}/nm (lg ε): 203.2 (4.67), 286.8 (3.73); λ_{min}/nm (lg ε): 256.8 (3.19). MS, *m*/*z*: 359 [M$^+$]. Found (%): C, 66.78; H, 6.98; N, 3.84. Calc. for $C_{20}H_{25}NO_5$ (%): C, 66.84; H, 7.01; N, 3.90.

†† Single crystals of **10** were obtained by crystallisation from ethanol. Crystallography for **10**: $C_{20}H_{25}NO_5$, monoclinic, space group $P2_1/n$, a = 8.259(2) Å, b = 25.434(4) Å, c = 8.855(2) Å, β = 102.98(2)°, V = 1812.5(7) Å^3, Z = 4, d_{calc} = 1.317 g cm^{-3} and μ = 0.94 cm^{-1}. X-ray diffraction data were collected at 293 K on a Nicolet R3m diffractometer (MoKα radiation) with $\omega/2\theta$ scans, $1.60 < \theta < 27.56°$. The structure was solved using the SIR97[13(a)] and refined using the SHELXL97[13(b)] crystallographic software. Refinement was converged with R_1 = 0.0439, wR_2 = 0.1181 [3286 reflections with $I > 2\sigma(I)$] and R_1 = 0.0562, wR_2 = 0.1278 for all data (4186 reflections), GOOF = 1.050. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/89.

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