[3+3] Cyclocondensation of 1-alkyl-substituted 3,4-dihydroisoquinolines with 2-aminomethylenecycloalkane-1,3-diones or aminomethylene malonates: a novel annelation reaction in the series of cyclic Schiff's bases

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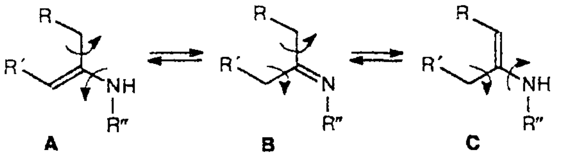
A new approach to the construction of polycyclic skeletons of fused azines with nitrogen at the bridgehead based on a novel reaction of cyclic Schiff's bases (1-alkyl-substituted 3,4-dihydroisoquinolines) with α-aminomethylenecarbonyl compounds (2-aminomethylenecyclohexane-1,3-diones or aminomethylenemalonic ester) was developed.

Key words: cyclic Schiff's bases, azomethines, 1-alkyl-3,4-dihydroisoquinolines, enamines, aminoenones, β-aminoacrylates, 2-aminomethylenecyclohexane-1,3-diones, aminomethylene malonates, benzo[*a*]quinolizines, dibenzo[*a,f*]quinolizinium chlorides, 8-aza-D-homogonanium chlorides, 8-azasteroids, [3+3]cyclocondensation, annelation.

Azomethines and their functional derivatives are known as valuable versatile substrates for fine organic syntheses.[1—13] Due to the characteristic imine—enamine tautomerism (A $\rightleftarrows$ B, B $\rightleftarrows$ C),[1,7,9] these isosters of carbonyl compounds can manifest dual reactivity and serve as nucleophiles (as enamino tautomers **A** and **C**) or electrophiles (imino tautomer **B**).

Scheme 1



At the same time, due to rotational C—C and C—N isomerism (in the absence of structural restrictions), azomethines are able to exist in several conformations only determined by stereoelectronic intra- and intermolecular interactions. This causes the high regio- and stereoselectivity of their reactions.[3,7,9] For these reasons, azomethines are widely used in syntheses both for constructing carbo-[1,2,4—7] and heterocyclic molecular skeletons[1—13] and for functionalization of the latter.[1—5,7—10] Nevertheless, it should be noted that their dual reactivity has almost never been used in cross reactions of enamines **A** and **C** with imines **B**. Only a few examples of syntheses[14—17] using the different reactivity of imines and enamines in their co-transformations are known to date.

In a continuation of our studies into the synthesis of fused heterocyclic nitrogen-containing compounds structurally related to isoquinoline alkaloids[14,18,19] and steroids[15,16,20—22] and in order to develop a simple and effective method for constructing such molecular structures, we studied the interactions of cyclic Schiff's bases and azomethines with β-dicarbonyl compounds and their enol derivatives, in particular, aza-derivatives.

In the present work we found that 1-alkyl-3,4-dihydroisoquinolines (**1a—c**), cyclic azomethines, react with aminomethylenecyclohexane-1,3-diones or aminomethylene malonates (**2a,b** and **3**), which are enamines or, more precisely, enaminones, to afford the corresponding 8-aza-D-homogonanium derivatives (**4a,b**) and benzo[*a*]quinolizines (**5a,b**) when their mixtures are heated in acetic acid and dimethylformamide. Regioisomeric derivatives **6** and **7** were not found, which indicates a high selectivity of the interaction (Scheme 2).

This reaction, which has not been described before, provides an exceptionally simple and convenient approach to a wide range of benzo[*a*]quinolizine derivatives and opens up possibilities for synthesizing various fused nitrogen-containing heterocycles with nitrogen atoms at the bridgeheads basing on readily available cyclic azomethines and functionalized enamines.

Compounds **4a,b** and **5a,b** obtained are undoubtedly of interest as intermediates in the syntheses of benzo[*a*]- and dibenzo[*a,f*]quinolizine derivatives that cannot be synthesized by known methods, as potential biologically active compounds promising for the development of new pharmacological preparations, and also as model structures in studies of structure—biological function interactions in the benzo[*a*]quinolizine series.

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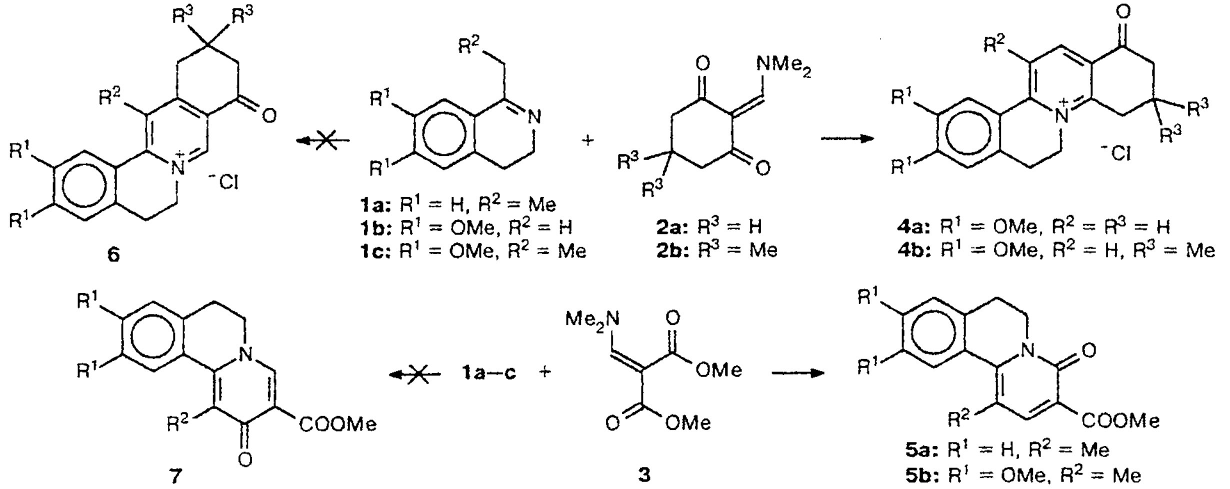
Scheme 2



Experimental

The reactions and individual products were monitored by TLC on Silufol UV-254 or Woelm silica gel plates (fixed layer) with a 8 : 1.5 : 0.5 chloroform—methanol—water mixture (for **4a,b** derivatives) and a 9.5 : 0.5 chloroform—methanol mixture (for **5a,b** derivatives) as eluents. The chromatograms were visualized by treatment with UV light or iodine vapors followed by heating at 250—350 °C. Melting points were determined on a Boetius hot stage. UV spectra were recorded on a Specord M-400 spectrophotometer. IR spectra were obtained on a UR-20 instrument. Mass spectra were recorded on a Schimadzu GC-17A/QP-5000 chromato-mass spectrometer with an ionization energy of 70 eV and direct injection of samples.

2,3-Dimethoxy-17a-oxo-6,7,15,16,17,17a-hexahydro-8-aza-D-homogonanium chloride (4a). A mixture of Schiff's base **1b** (2.05 g, 10 mmol) and aminovinyldiketone **2a** (1.67 g, 10 mmol) in glacial acetic acid (6 mL) was refluxed for 2 h in an argon atmosphere. The reaction mixture was evaporated, and the residue was dissolved in water (5 mL) and extracted with chloroform. The extracts were discarded, and concentrated HCl (1 mL) was added to the aqueous phase. Then sodium chloride was added to the solution until saturation, and the solution was again extracted with chloroform. The extracts were dried with Na_2SO_4, filtered, and concentrated to 10—15 mL. The target product was precipitated with hexane to afford 2.94 g (85 %) of 8-aza-D-homogonanium derivative **4a** as yellow crystals with m.p. 225—227 °C (dec.) from a chloroform—hexane mixture. Found (%): C, 65.83; H, 5.69; Cl, 10.37; N, 3.92. $C_{19}H_{20}ClNO_3^+$. Calculated (%): C, 65.99; H, 5.83; Cl, 10.25; N, 4.05. MS, *m/z*: 310 $[M-Cl]^+$. UV (EtOH), λ_{max}/nm: 235 (7650), 279.2 (6870), 304.6 (8730), 397.9 (18670). IR (KBr), ν/cm^{-1}: 3600—3200, 1692, 1595, 1556, 1487, 1366, 1301, 1278, 1255, 1223, 864, 820, 795, 776.

16,16-Dimethyl-2,3-dimethoxy-17a-oxo-6,7,15,16,17,17a-hexahydro-8-aza-D-homogonanium chloride (4b) was synthesized by a procedure similar to that described for **4a** starting from a mixture of Schiff's base **1b** (1.54 g, 7.5 mmol) and aminovinyldiketone **2b** (1.46 g, 7.5 mmol) in glacial acetic acid (5 mL). Refluxing the mixture for 1.5 h afforded 2.54 g (90 %) of 8-aza-D-homogonanium derivative **4b** as bright yellow crystals, m.p. 229—231 °C (dec.) from a chloroform—hexane mixture. Found (%): C, 67.03; H, 6.78; Cl, 9.51; N, 3.51. $C_{21}H_{24}ClNO_3^+$. Calculated (%): C, 67.16; H, 6.89; Cl, 9.44; N, 3.73. M 375.58. MS, *m/z*: 340 $[M-Cl]^+$. UV (EtOH), λ_{max}/nm: 205.5 (39230), 235.5 (8540), 278.2 (8060), 306.4 (9470), 398.7 (19220). IR (KBr), ν/cm^{-1}: 3600—3200, 1695, 1597, 1558, 1488, 1360, 1309, 1282, 1257, 1235, 1156, 880—870, 800, 759.

1-Methyl-3-methoxycarbonyl-4*H*-6,7-dihydrobenzo[*a*]quinolizine-4-one (5a). A mixture of Schiff's base **1a** (0.8 g, 5 mmol) and dimethyl dimethylaminomethylene malonate **3** (0.95 g, 5 mmol) in dry DMF (2 mL) was heated in an argon atmosphere at 160—190 °C for 17 h. The reaction mixture was then evaporated under reduced pressure, and the residue was dissolved in chloroform, washed with water, dried with Na_2SO_4, and concentrated. The residue was flash-chromatographed on silica gel (10 g, 5/40 mm) with chloroform as the eluent to obtain 1.05 g (82 %) of benzo[*a*]quinolizine **5a** as white crystals, m.p. 146.5—148 °C (from a chloroform—hexane mixture). Found (%): C, 75.12; H, 5.87; N, 5.37. $C_{16}H_{15}NO_3$. Calculated (%): C, 75.28; H, 5.92; N, 5.49. MS, *m/z*: 255 $[M]^+$. UV (EtOH), λ_{max}/nm: 260.8 (23930), 307.7 (12250), 371.2 (22150). IR (KBr), ν/cm^{-1}: 1725, 1613, 1530, 1482, 1225.

1-Methyl-9,10-dimethoxy-3-methoxycarbonyl-4*H*-6,7-dihydrobenzo[*a*]quinolizine-4-one (5b) was synthesized by a procedure similar to that described for derivative **5a** starting from a mixture of Schiff's base **1c** (1.03 g, 5 mmol) and dimethyl dimethylaminomethylene malonate **3** (1.18 g, 5.5 mmol) in DMF (2 mL). Heating the mixture at 170 °C for 9 h afforded 1.24 g (78.5 %) of benzo[*a*]quinolizine **5b** as white crystals, m.p. 222 —224°C (from a chloroform—hexane mixture). Found (%): C, 64.54; H, 5.28; N, 4.23. $C_{17}H_{17}NO_5$. Calculated (%): C, 64.75; H, 5.43; N, 4.44. MS, *m/z*: 315 $[M]^+$. UV (EtOH), λ_{max}/nm: 382.8 (26780). IR (KBr), ν/cm^{-1}: 1728, 1549, 1514, 1472, 1438, 1375, 1282, 1263, 1221, 1162, 1120.

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