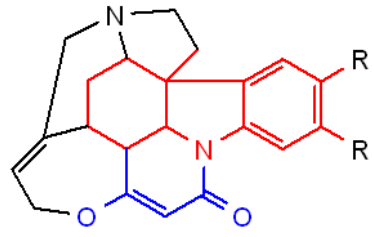
Syntheses of 8,9,10,11-Tetrahydro-pyrido[3,2,1-jk]carbazoles, 1,2,3, 11b-Tetrahydro-pyrido[3,2,1-jk]carbazoles and 7a,8,9,10,11,11a-Hexahydro-pyrido[3,2,1-jk]carbazoles

Wolfgang STADLBAUER * **Hoai V. DANG, Ali DEEB, Birgit SCHUKI, Thomas KAPPE**

Institut für Chemie, Organic Synthesis Group,
Karl-Franzens-University of Graz
Heinrichstrasse 28, A-8010 Graz (Austria)

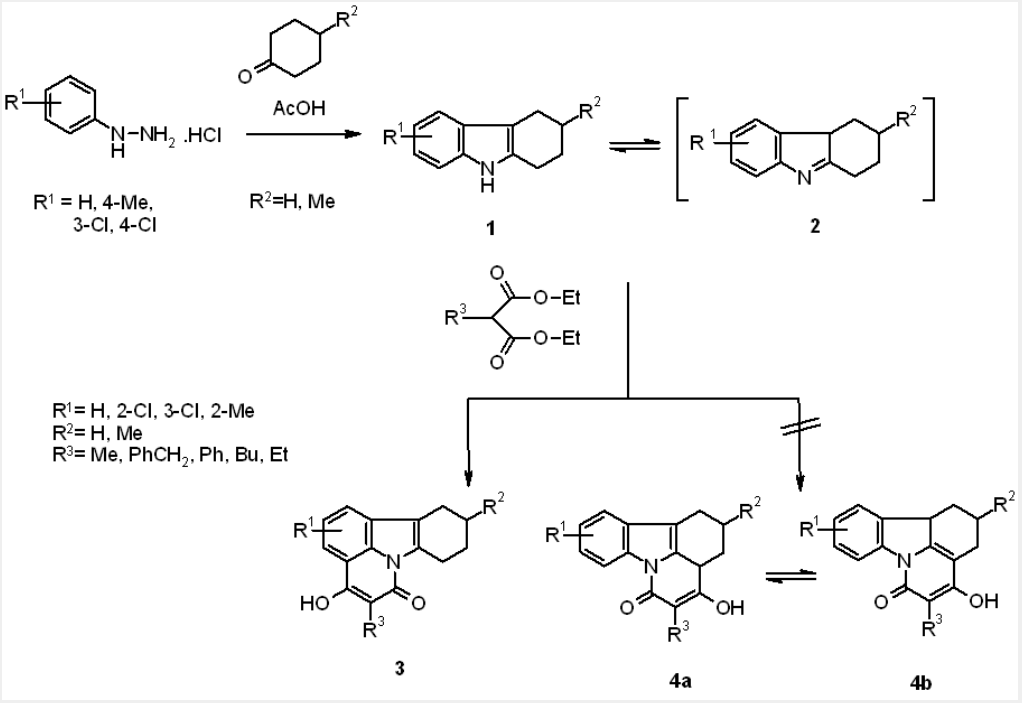
E-mail: wolfgang.stadlbauer@uni-graz.at

General Aspects



Pyrido[3,2,1-jk]carbazol-6-one in its partial hydrogenated form is part of the heterocyclic skeleton of many natural products (e. g. strychnos alkaloids such as strychninolones and brucinolones, picrasidin Q and olivacin alkaloids). It possesses the biological interesting combination of an indole structure and of a 2-quinolone; Comparison with strychnos alkaloids shows that it has already four rings and two oxygen functions in the correct position. [1] .

Synthesis of 2,3,4,9-Tetrahydro-1H-carbazoles
Ring Closure Reaction to 8,9,10,11-tetrahydro-pyrido[3,2,1-jk]carbazol-6-ones

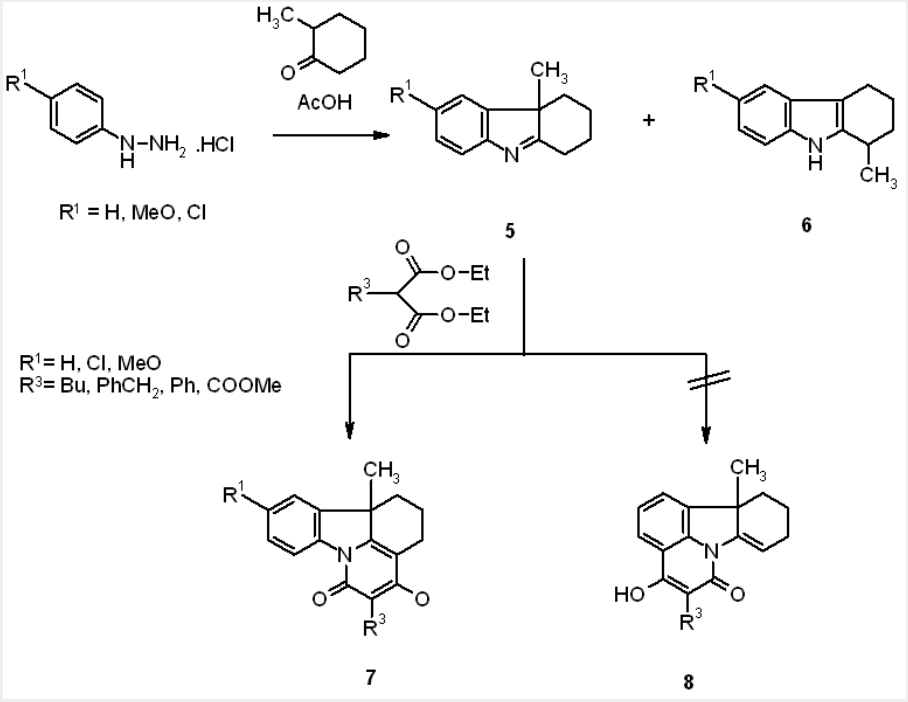


In the literature several syntheses for 2,3,4,9-tetrahydro-1H-carbazoles **1** (sometimes named incorrectly 1,2,3,4-tetrahydrocarbazoles) are described, starting either directly from cyclohexanones and phenylhydrazines, or from similar derivatives and intermediates; also the hydrogenation of carbazoles is described [2].

For our purposes, which were directed to the easy and regioselective introduction of electron-pushing and pulling substituents, we started from phenylhydrazine derivatives such as 3- and 4-chlorophenylhydrazine, and cyclohexanone or methylcyclohexanone using the general type of a *Fischer-Indole-Synthesis* in glacial acetic acid. The yields were dependent on the electron and steric influence of the substituents in the aromatic ring and ranged between 40 and 85%.

The cyclization to pyridocarbazoles (**3** or **4**) was achieved by thermal condensation with diethyl malonates at about 250 °C similar to the reactions investigated in the carbazoles series [3]. The direction of the second step of the cyclization proceeded with R^2 = H and methyl to the electron rich and reactive aromatic ring and gave **3** by electrophilic aromatic substitution of the ketene intermediates of malonates as found in a series of similar reactions [4]. Now the question raised if the cyclization of electron-deficient tetrahydrocarbazoles with R^1 = chloro gives the same pyridocarbazoles of type **3** starting from tautomers **1**, or - if the reaction starts from the second possible carbazole tautomer of type **2** to give (at least as by-product) pyridocarbazoles of type **4**. Careful work-up of the reaction mixture, however, gave in all cases only one detectable product of a pyridocarbazole (however, in lower yields), which could be assigned unequivocal to the structure of type **3** by ^{1}H-nmr spectral methods and comparison with **7**.

Synthesis of 2,3,4,4a-Tetrahydro-1H-carbazole
Ring Closure Reaction to 1,2,3,11b-Tetrahydro-pyrido[3,2,1-jk]carbazol-6-ones

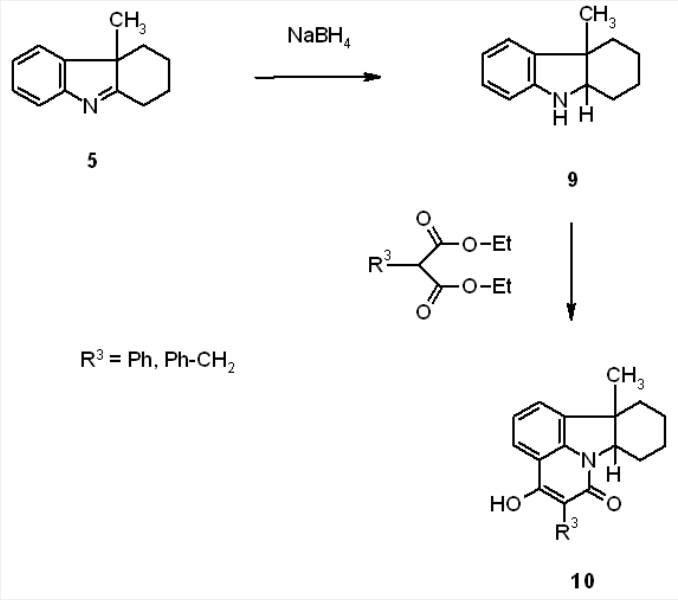


4a-Methyl-2,3,4,4a-tetrahydro-1H-carbazole **5** was obtained from 2-methylcyclohexanone and phenylhydrazine together with its 1-methyl isomer **6**, probably via a rearrangement reaction, adopting known methods [5]. Such a rearrangement hypothesis could explain why isomer **2** or its cyclization products **4** are not formed during the reaction from **1** to **3**.

Both isomers, **5** and **6**, have different properties (neutral and basic), which allows a simple separation e.g. by extraction in basic media. The ratio of both isomers can be influenced by the application of different acids, however the yields werde moderate. The influence of electron-pushing and pulling substituents such as methoxy or chloro was visible, surprisingly shifting to higher yields with the chloro substituent, and to lower yields with the methoxy group.

The cyclocondensation reaction of **5** with malonates at about 250 °C gave in moderate yields the pyridocarbazoles **7** by ring closure reaction at the more reactive enamine double bond (9a,1) at position 1; no cyclization reaction could be observed directed to the aromatic ring which should give pyridocarbazoles such as products **8**; there was no influence observed in the ring closure reaction deriving from substituents R^1.
The structural assignment could be performed by ^{1}H-nmr spectral methods.

Synthesis of 2,3,4,4a,9,9a-Hexahydro-1H-carbazole
Ring Closure Reaction to 7a,8,9,10,11,11a-Hexahydro-pyrido[3,2,1-jk]carbazol-6-one



The regioselective reduction of the enamine double bond in 4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole **5** could be achieved with sodium borohydride to give 4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole **9**; there was a mixture of two diastereomeric compounds visible in the isolated product (probably mainly the cis-isomer and in less than 5% the trans isomer). This mixture was not separated and used for further reactions.

The carbazole **9** behaves in the cyclocondensation reaction with malonates like a N-substituted aniline and gives in good yields the corresponding 4-hydroxy-5,11a-dimethyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-jk]carbazol-6-ones **10** by attack of the intermediate ketene derivative at the adjacent aromatic ring position.

This ring system has already the correct hydrogenation degree as visible in strychnin, however in the reverse sequence.

Further reactions for functionalization of these pyridocarbazoles lead to biologically active compounds. This work is in progress.

Experimental

General procedure for the synthesis of tetrahydro-1H-carbazoles (**1, 5**).
To a suspension of anhydrous sodium acetate and the corresponding cyclohexanone in glacial acetic acid, the corresponding phenylhydrazine hydrochloride in glacial acetic acid was added in small portions. The reaction mixture was heated for some hours, then cooled, diluted with water and filtered (for **5**, the reaction mixture was made alkaline and then extracted with diethylether and purified by distillation).

General procedure for the synthesis of 5-alkyl- or 5-aryl-4-hydroxy-pyrido[3,2,1-jk]carbazole-6-ones (**3, 7, 10**).
An equimolar mixture of the appropriate alkyl- or arylmalonate and the corresponding carbazole (**1, 5** or **9**) in diphenylether was heated under reflux. During this period ethanol was liberated. Then the excess of diphenylether was removed, the residue triturated with hexane and filtered by suction. The solid product was dissolved in aqueous sodium hydroxide and filtered from insoluble products. The filtrate was extracted with toluene, cleared with norite and acidified with conc. hydrochloric acid; the solid was filtered and then washed with water.

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