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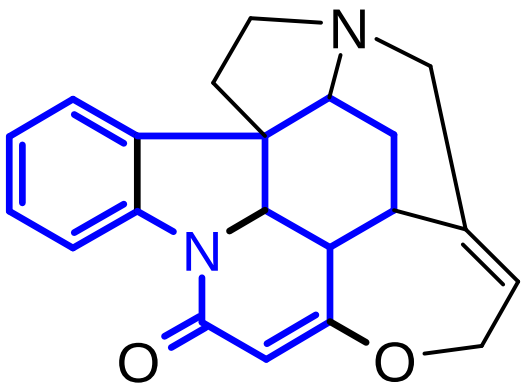
Syntheses, Substitution and Cyclization Reactions of 7a,8,9,10,11a-Hexahydro-pyrido[3,2,1-*jk*]carbazoles With a Strychnos Alkaloids Partial Structure



Hexahydropyrido[3,2,1-*jk*]carbazol-6-one (**blue partial structure**) is part of the heterocyclic skeleton of many natural products (e. g. Strychnos alkaloids such as strychninolones and derivatives).

Hexahydropyrido[3,2,1-*jk*]carbazol-6-one possesses the biological interesting combination of the well-known indole structure and the 4-hydroxy-2-pyridone structure, which can be found in a number of natural products.

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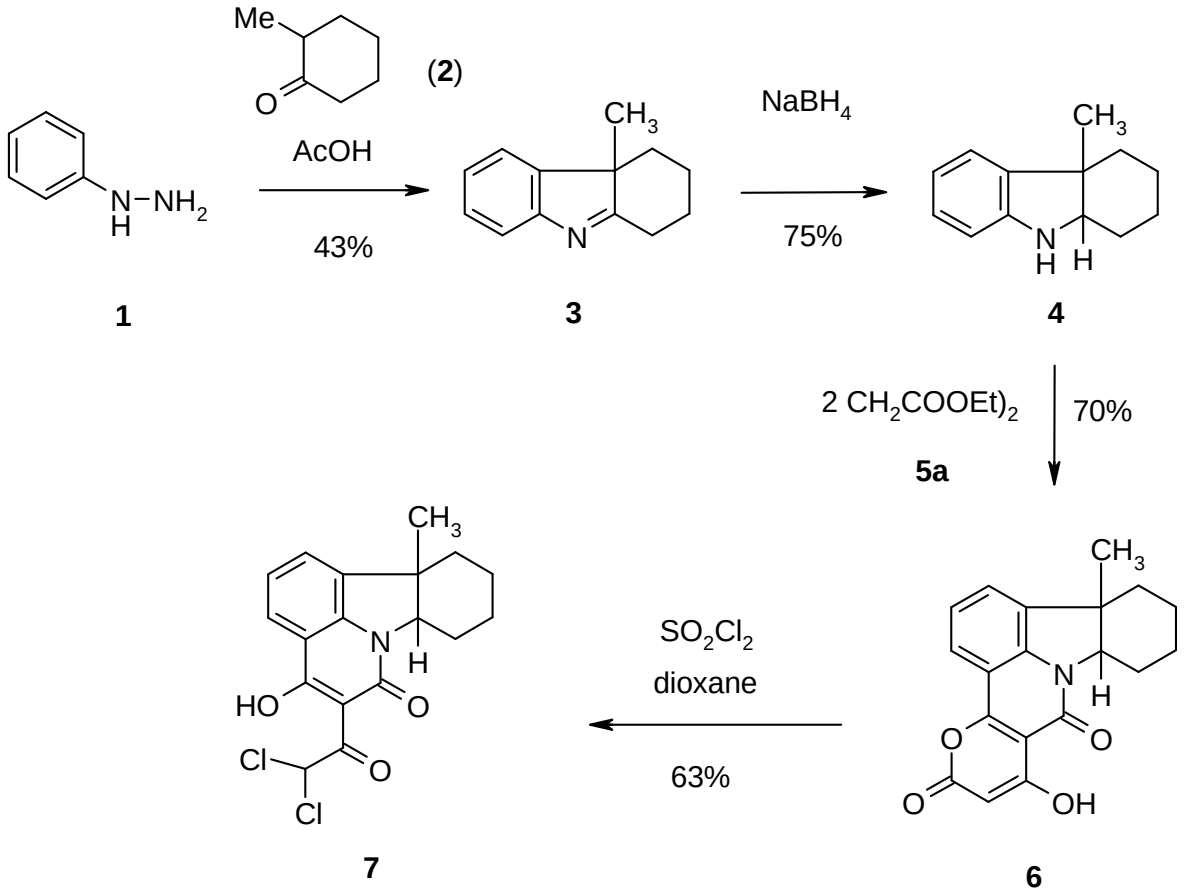

Tetrahydrocarbazole **3**, obtained from phenylhydrazine hydrochloride (**1**) and 2-methyl-cyclohexanone (**2**), was regioselectively reduced with sodium borohydride to hexahydrocarbazole **4**.

Cyclocondensation of **4** with 2 molecules of diethyl malonate (**5a**) gives 7-hydroxy-hexahydro-pyranopyrido-carbazoledione **6**, which affords on chlorination with sulfuryl chloride by ring opening 5-dichloroacetyl-hexahydro-pyridocarbazolone **7.**

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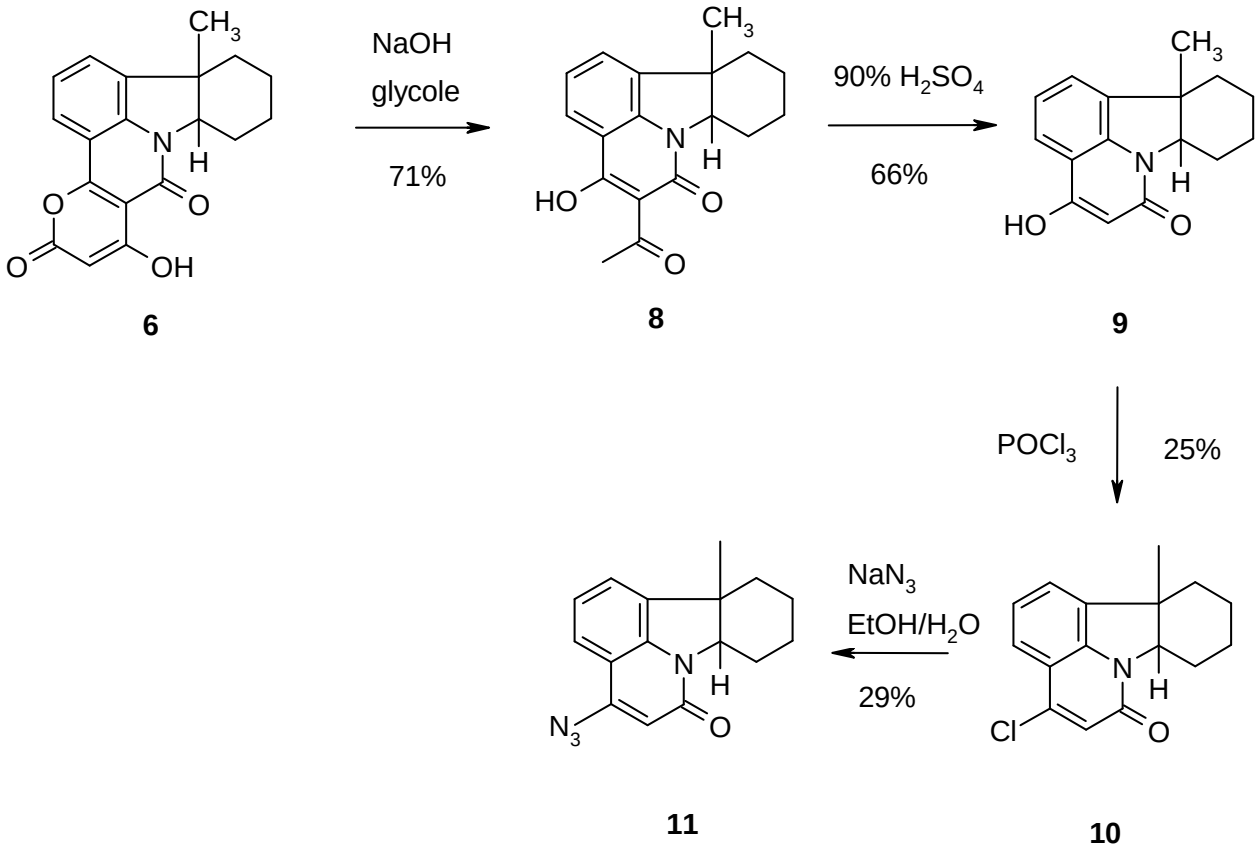

Ring opening of **6** with sodium hydroxide yields 5-acetyl-tetrahydro-pyridocarbazolone **8**. The 5-acetyl group in **8** is removed with 90% sulfuric acid and yields highly pure 5-unsubstituted 4-hydroxy-hexahydro- pyrido-carbazolone **9**. Chlorination at position 4 can be carried out with phosphoryl chloride by exchange of the 4-hydroxy group to form **10**. Azidation of **10** at position 4 can be performed in ethanol/water to give **11**.

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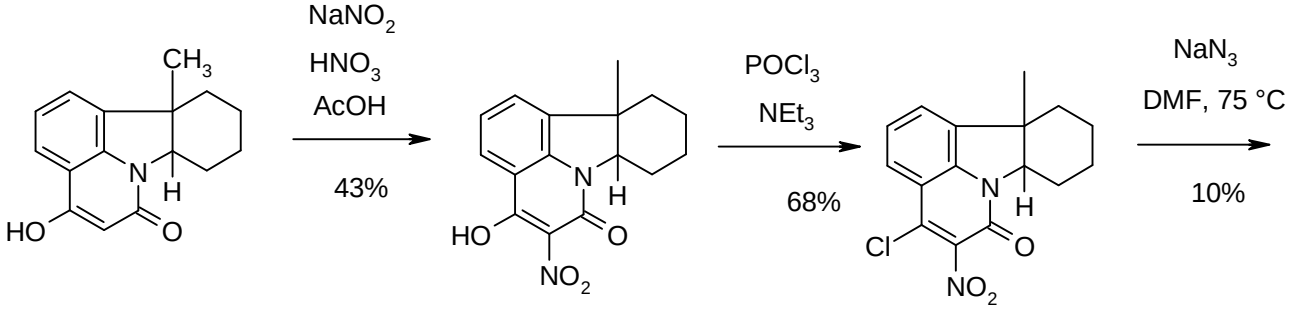
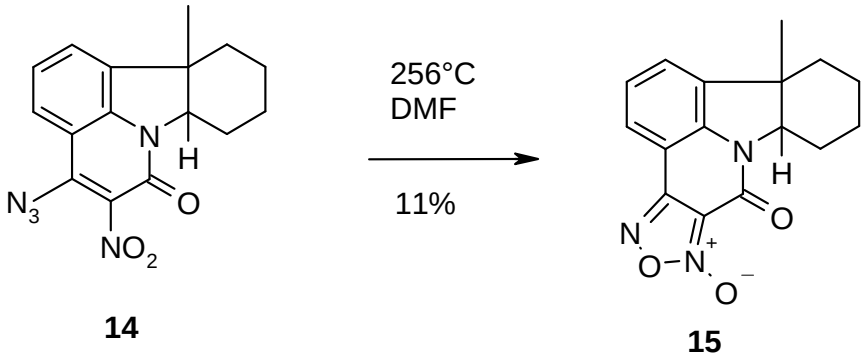


9 **12** **13**



14 **15**

Nitration of hexahydro-pyridocarbazole **9** with nitric acid catalyzed by a small amount of sodium nitrite gives pure 5-nitro-hexahydro-carbazolone **12** in moderate yields without side reactions by attack at the benzo part of the molecule.

Halogenation of **12** to chloro derivative **13** needs the addition of triethylamine to cleave the hydrogen bonding between hydroxy and nitro group, which hinders the attack of phosphoryl chloride. Azidation of **13** forms 4-azido-hexahydro-pyridocarbazole **14**.

Thermolyis of the azide **14** forms by cyclization the furoxane **15**. The thermal reaction conditions of this reaction were studied by DSC (differential scanning calorimetry)

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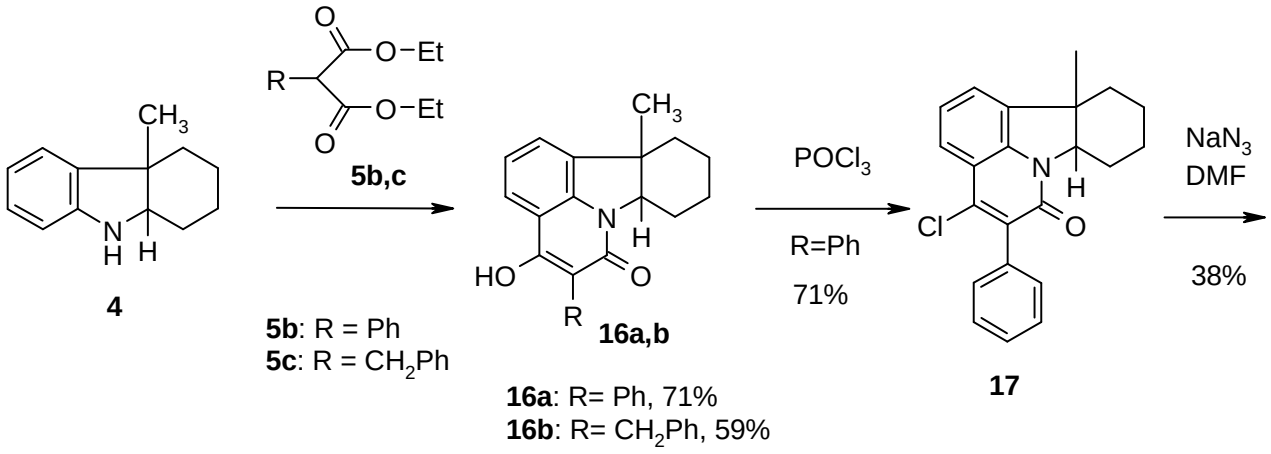

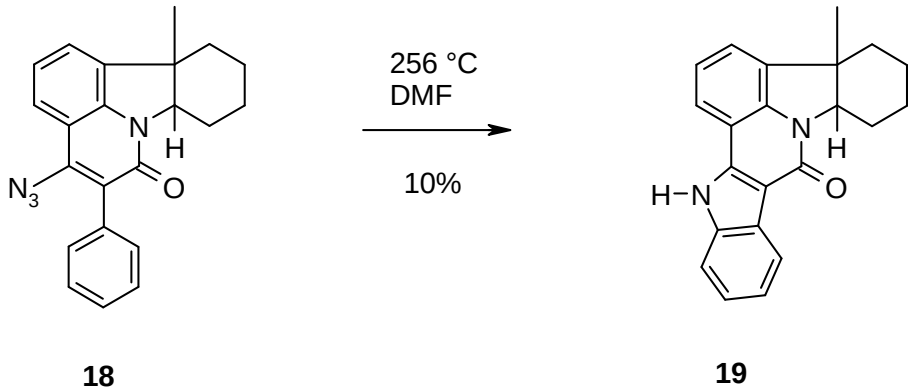

Cyclocondensation of **4** with alkyl-or phenyl-malonates **5b,c** give 4-hydroxy-hexahydro-pyridocarbazol-6-one **16**.

Subsequent chlorination and azidation of **16** at position 4 forms chloro derivative **17** and azide **18**.

Thermolysis of the azide **18** forms by cyclization via a nitrene intermediate the indole derivative **19**. The thermal decomposition was studied by DSC.

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Conclusion

This investigation shows that the reduction of tetrahydrocarbazole **3** with sodium borohydride leads in good yields to hexahydrocarbazole **4**. Cyclocondensation of **4** with diethyl malonate (**5a**) or alkyl/arylmalonates **5b,c** results after a 3-step reaction in the formation of pyridocarbazoledione **9** or 5-alkyl- or aryl-hexahydropyridocarbazolones **16a,b**.

5-Unsubstituted 4-hydroxy-hexahydropyridocarbazolone **9** gave on nitration the 5-nitro derivative **12** which was further transformed to the reactive 4-azido-5-nitro-hexahydropyridocarbazolone **14**. Thermolyis resulted in a ring closure reaction to the furoxane **15**.
4-Azido-5-phenyl-hexahydropyridocarbazolone **18** obtained from **16a** formed by thermal cyclization via a nitrene intermediate hexahydro-indolo-pyridocarbazolone **19**.

The thermolytical conditions of both cyclization reactions were investigated by differential scanning calorimetry (DSC).