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Tiina Putkonen

TEKNILLINEN KORKEAKOULU
TEKNISKA HÖGSKOLAN
HELSINKI UNIVERSITY OF TECHNOLOGY
TECHNISCHE UNIVERSITÄT HELSINKI
UNIVERSITE DE TECHNOLOGIE D'HELSINKI

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Dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the Department of Chemical Technology for public examination and debate in Auditorium Ke 2 at Helsinki University of Technology (Espoo, Finland) on the 23th of January, 2004, at 12 noon.

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Abstract

Methods to synthesise substituted pyridine derivatives utilising 1,4-dihydropyridines were studied. Addition of nucleophiles to *N*-alkyl pyridinium salts and application of the products to alkaloid synthesis were investigated.

Application of the Kröhnke procedure to the synthesis of indole alkaloids is described. The feasibility of applying the Kröhnke procedure to pyridine derivatives without an electron withdrawing β-substituent at the pyridinium ring was demonstrated by adding dimethyl malonate to the γ-position of Boc protected 1-[2-(3-indolyl)ethyl]pyridinium salts. The method permits access to the indoloquinolizidine skeleton present in several indole alkaloids.

The total synthesis of (±)-tangutorine, a novel indole alkaloid, was achieved. The dithionite reduction leading to a 1,4-dihydropyridine derivative provided easy access to the tangutorine skeleton with good yields.

In a second part of the work, dihydropyridines were stabilised through the introduction of cyanide ion to iminium intermediates. The Polonovski–Potier reaction and the cyano-trapping method were used in the preparation of dimethyl malonyl substituted indolo[2,3-α]quinolizidine derivative, a potential synthon of antirhine.

A novel synthetic approach to the preparation of 2,6-dicyanopiperidine derivatives via 1,4-dihydropyridine intermediates was examined. The formation of 2,6-dicyanopiperidines in the Fry reaction was verified. The stereochemistry of 2,6-dicyanopiperidine derivatives is discussed.

Preface

This thesis is based on experimental work carried out during the years 1997-2002 in the Laboratory of Organic Chemistry, Helsinki University of Technology, Espoo, Finland.

I am deeply indebted to Professor Reija Jokela for her encouragement and guidance during all phases of the work. I also wish to express my sincere gratitude to Professor Mauri Lounasmaa, under whose leadership this project was begun. Special thanks are due to Docent Arto Tolvanen for his valuable advice and co-operation and to Professor Ari Koskinen for providing the necessary facilities for carrying out this work.

Warm and sincere thanks are owed to many others: to my co-authors Dr. Pirjo Hanhinen and Emmi Valkonen, to Kimmo Karinen for performing the HR spectral analyses, to Anna-Maija Horko for performing the CHN analysis and for skilful experimental work. Not of least importance, the entire personnel of the Laboratory of Organic Chemistry contributed to the creation of a pleasant environment in which to work.

Financial support from the Helsinki University of Technology and the Finnish Foundation of Technology is gratefully acknowledged.

Above all, loving thanks to my husband, Matti, for his patience, support and encouragement during the years it took to complete this work, and to our son Niko for revitalising my spirits when this was most needed.

Helsinki, September 2003

Tiina Putkonen

List of publications

The thesis consists of a summary review and the following publications:

I Hanhinen, P., Putkonen, T. and Lounasmaa, M., Direct introduction of nucleophilic carbanions to the γ–position of N_a-Boc protected N_b-tryptophyl salts, without electron withdrawing substituents at the β-position, *Heterocycles* **51** (1999) 785-794.

II Hanhinen, P., Putkonen, T. and Lounasmaa, M., General strategies in the preparation of antirhine-type indole alkaloids, *Heterocycles* **51** (1999) 1827-1842.

III Putkonen, T., Valkonen, E., Tolvanen, A. and Jokela, R., 1,4-Dihydropyridine equivalents: A novel approach to 2,6-cyanopiperidine derivatives, *Tetrahedron* **58** (2002) 7869-7873.

IV Putkonen, T., Tolvanen, A. and Jokela, R., First total synthesis of (±)-tangutorine, *Tetrahedron Lett.* **42** (2001) 6593-6594.

V Putkonen, T., Tolvanen, A., Jokela, R., Caccamese, S. and Parrinello, N., Total synthesis of (±)-tangutorine and chiral HPLC separation of enantiomers, *Tetrahedron* **59** (2003) 8589-8595.

Papers I-V are referred to in the text by their Roman numerals.

The author's contribution

Publication I	The author did the experimental work. Interpretation of the results and writing of the article were carried out by the co-authors.
Publication II	The author did the experimental work. Interpretation of the results and writing of the article were carried out by the co-authors.
Publication III	The author did the experimental work except for the Fry reactions, which were done together with the co-authors. The author interpreted the results and wrote the article.
Publication IV	The research plan for the experimental work was drawn up by the author together with the co-authors. The author was responsible for the experimental work and writing of the article.
Publication V	The research plan for the experimental work was drawn up together with the co-authors. The author was responsible for the experimental work and writing of the article except for the part related to the separation of enantiomers.

Contents

1 Introduction

No class of naturally occurring organic substances shows such an enormous range of structures as the alkaloids.[1] One of the largest subgroups of these nitrogen containing natural products is the monoterpenoid indole alkaloids. With the wide-ranging pharmacological activities of alkaloids, their synthesis is of great interest.

The piperidine ring is a characteristic feature of a large number of alkaloids. The development of general methods for the functionalization of this ring system has therefore become an important synthetic challenge. In many synthetic routes towards indole alkaloids of indoloquinolizidine type, the most tedious and intellectually least attractive part of the work has been the preparation of pyridine derivatives appropriately substituted at α-, β- and γ-positions. Methods that permit direct introduction of substituents into simpler and more easily accessible intermediates are thus attractive alternatives. Most of the synthetic attempts in this direction have involved the use of dihydropyridines, the idea being to exploit the enamine / imine (iminium salt) equilibrium that is characteristic of these species to effect additions with electrophiles and nucleophiles, respectively.

Three routes have generally been pursued to prepare dihydropyridines: (a) synthesis from appropriately functionalized ring-opened precursors (b) reaction of pyridines or their salts with nucleophiles and (c) partial reduction of pyridines or their salts.[2] In this work the latter two routes were closely examined.

The instability of some dihydropyridinium salts may cause difficulties in their utilization. The introduction of cyanide ion to iminium intermediates produces α-amino nitriles. These cyano-masked iminium ions retain their reactivity and are more stable than the corresponding dihydropyridinium salts. Possibilities to synthesise pyridine derivatives and 2,6-dicyanopiperdines via 1,4-dihydropyridine stage and methods taking advantage of cyano-masked iminium ions were investigated in this work.

The biogenetic numbering, introduced by Le Men and Taylor,[3] is applied here to naming indole alkaloids and their derivatives. In the case of tangutorine (**1**), a novel indole alkaloid, we have suggested a numbering[4,V] based on the biogenetic numbering. For other compounds the IUPAC numbering[5] is used (Figure 1).

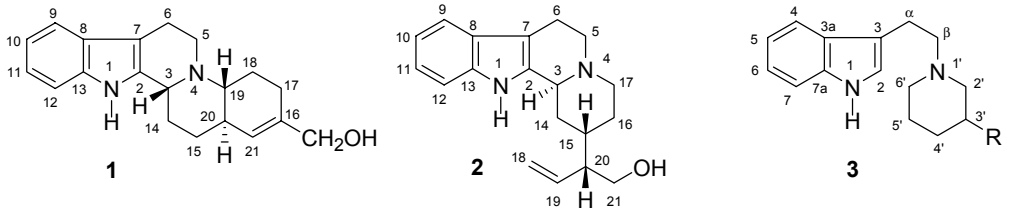


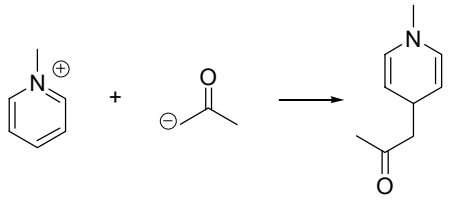
Figure 1. Structures of tangutorine (**1**) and antirhine (**2**) (biogenetic numbering system)[3] and 1'-[2-(3-indolyl)ethyl]piperidine **3** (IUPAC numbering system)[5].

2 1,4-Dihydropyridines

The addition of nucleophiles to α- and γ- positions of *N*-substituted pyridinium salts gives 1,2- and 1,4-dihydropyridines, respectively. The regioselectivity of the addition reaction depends on the hardness of the nucleophile: hard nucleophiles preferentially attack at C-2 whereas soft ones attack at C-4. The addition is also believed to proceed at both the α- and γ-carbon centres under kinetic control and only at the γ-carbon under thermodynamic control.[6] The Kröhnke procedure[7–9] and sodium dithionite reduction[10–12] are examples of reactions involving addition of nucleophiles at γ-position. The 1,4-dihydropyridines formed in these reactions can be used as intermediates in several indole alkaloid syntheses.

2.1 Kröhnke procedure

The Kröhnke procedure,[7–9] consisting of base-catalysed condensation of ketones with *N*-alkyl or *N*-acyl pyridinium salts, was investigated years ago (Scheme 1). It is of particular synthetic interest since it constitutes a useful method of forming new carbon–carbon bonds to give substituted 1,4-dihydropyridines.[6]



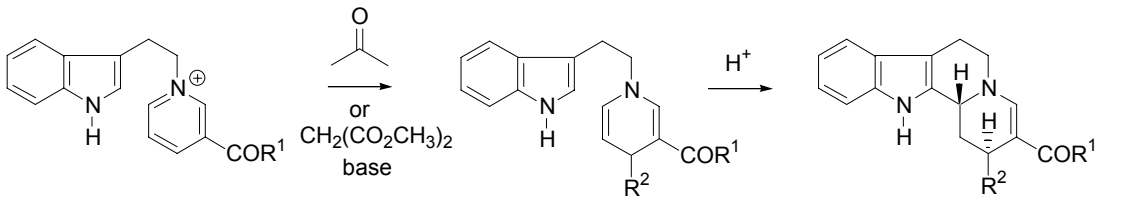
Scheme 1. An example of the Kröhnke procedure.

2.1.1 Applications to indole alkaloids

Later on, the Kröhnke procedure was adapted for the preparation of indoloquinolizidine derivatives.[6,13] Despite the generally low yields (20–30%), it has been used for the preparation of several heteroyohimbine derivatives.[14–16] One limitation of the method has been the need for an electron withdrawing substituent at the β-position of the pyridinium ring. This β-substituent increases the electrophilicity of the pyridinium ring in the nucleophilic addition step and stabilizes both the dihydropyridines resulting from γ-addition and the enamine unit in the final cyclized product.[6] Unfortunately, the introduction of an electron withdrawing substituent to the β-position often requires supplementary steps, which lower the overall yield.

Wenkert *et al.*[17] applied the Kröhnke procedure for the synthesis of yohimboid, ajmalicinoid and corynanthoid indole alkaloids. They replaced the earlier two-step reaction, the sodium dithionite reduction of pyridinium salts followed by mild acid treatment, by the simpler γ-substituent introduction by the Kröhnke procedure.

They proceeded with base-induced condensation of salts **4a**–**c** with acetone followed by acid treatment of intermediates **5**, producing compounds **6a**–**c** (Scheme 2). Because of the low yields of the ketones (**6a** 23%, **6b** 10%, **6c** 7%)[18] the acetonyl group was changed to a more amenable γ-substituent, dimethyl malonate. The yields were indeed better (**7a** 11%, **7b** 29%, **7c** 34%). However, there were difficulties with reversibility of the first reaction (**4**→**5**) and with the tendency for fragmentation of the intermediate into the pyridine salt precursors in the second reaction (**5**→**7**). The yield of tetracycle **7b** was later improved to 40% by modification of the experimental procedure.[19]



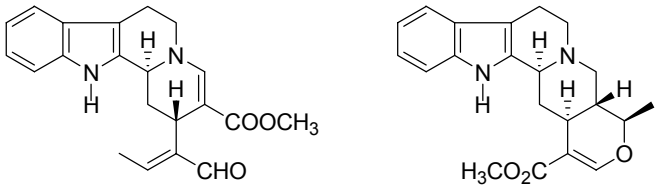
4a R^1=H
4b R^1=CH_3
4c R^1=OCH_3

5

6a R^1=H R^2=CH_2Ac
6b R^1=CH_3 R^2=CH_2Ac
6c R^1=OCH_3 R^2=CH_2Ac
7a R^1=H R^2=$CH(CO_2CH_3)_2$
7b R^1=CH_3 R^2=$CH(CO_2CH_3)_2$
7c R^1=OCH_3 R^2=$CH(CO_2CH_3)_2$

Scheme 2. Application of the Kröhnke procedure to the preparation of indole alkaloids.[17]

Acetonyl derivatives **6a**, **6b** and **6c** can be considered as simplified analogues of vallesiachotamine (**8**), and the tetracycle **7b** appeared to be an ideal intermediate for the synthesis of ajmalicinoid alkaloids, for example ajmalicine (**9**) (Figure 2).[17]



8 **9**

Figure 2. Structures of vallesiachotamine (**8**) and ajmalicine (**9**).

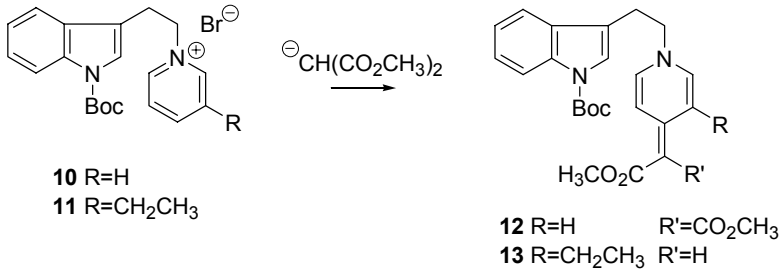
The Kröhnke reaction of pyridinium salts without an electron withdrawing group at the β-carbon suffers from deep-seated difficulties. The regiospecificity of both the addition and cyclization steps is difficult to predict. The stabilities of 1,4-dihydropyridines in air and of a cyclized product in the acid medium in which it is produced are dubious. Wenkert and his co-workers[17] were unable to isolate tractable amounts of products from the reaction of β-ethyl pyridinium salt with sodium malonate under a wide range of conditions.

2.1.2 Modification of the Kröhnke procedure

Even though it seemed that much of the success in the synthesis of pyridine derivatives involving vinylogous amides was associated with the presence of an electron withdrawing substituent at β-position, we decided to explore the possibility of using the Kröhnke

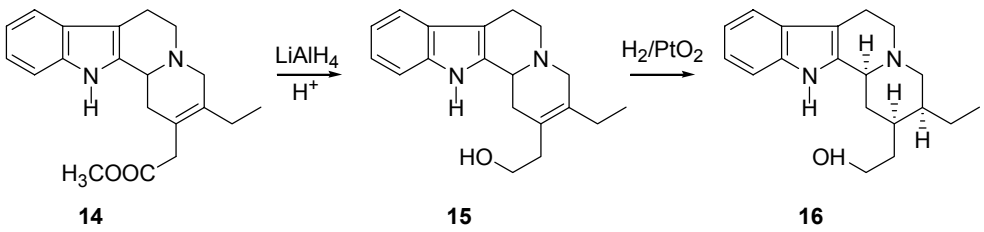
procedure for the direct introduction of carbanions to the γ-position of pyridinium salts without a substituent or with an alkyl substituent at the β-position.[I] This method would not require any preliminary preparation of the appropriate pyridine derivatives.

We used[I] two *N*-Boc protected salts as starting material: 1'-[2-(3-indolyl)ethyl]pyridinium salt (**10**) and 1'-[2-(3-indolyl)ethyl]-3'-ethyl-pyridinium salt (**11**). The addition of sodium malonate to salt **10** afforded compound **12** in 24% yield and the analogous reaction with salt **11** afforded, after spontaneous decarbomethoxylation, compound **13** in 32% yield (Scheme 3).



Scheme 3. Modification of the Kröhnke procedure for pyridinium salts without an electron withdrawing substituent.[I]

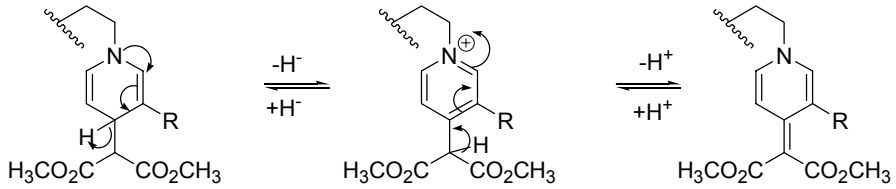
After a few following reactions from compound **13** (deprotection, reduction and acid treatment)[I] the useful indolo[2,3-α]quinolizidine intermediate **14** was obtained. After reduction of compound **14** with $LiAlH_4$ the analogous alcohol intermediate **15** was formed. Compound **15** can be reduced, for example to (±)-corynantheidol (**16**) (Scheme 4).[20]



Scheme 4. Intermediates **14** and **15** for preparation of (±)-corynantheidol (**16**).[20]

In general, in the absence of the electron withdrawing β-substituent, the equilibrium of the addition reaction is highly unfavourable for 1,4-dihydropyridines.[21] However, our results indicate that the oxidation state of the primary addition products changes, and the

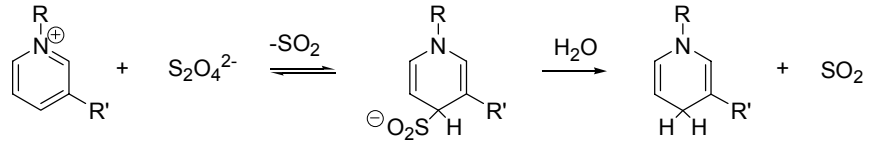
equilibrium is shifted towards the 1,4-dihydropyridines (Scheme 5). Despite the relatively low total yields, this simple method offers an alternative method for the total synthesis of several indole alkaloids.



Scheme 5. A possible mechanism for the Kröhnke procedure without an electron withdrawing substituent.[I]

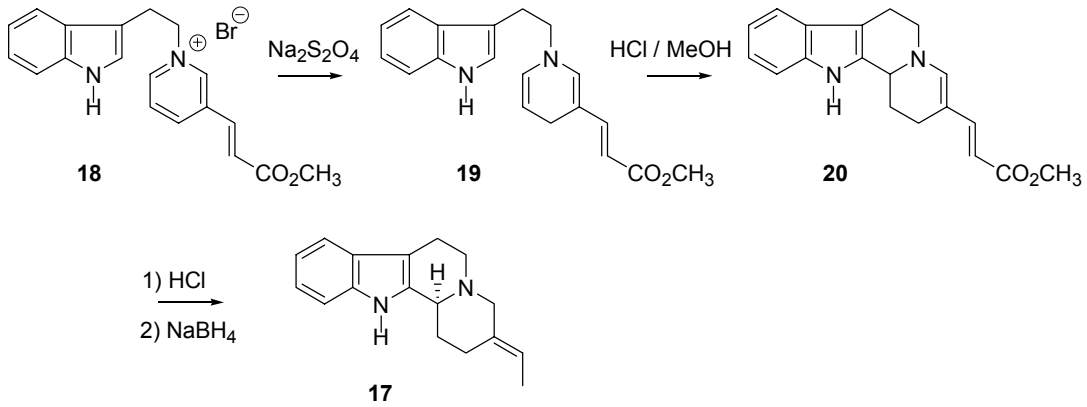
2.2 Dithionite reduction

Another synthetic route affording 1,4-dihydropyridines is the sodium dithionite ($Na_2S_2O_4$) reduction of *N*-alkyl pyridinium salts with electron withdrawing substituents at the β-position.[10–12] The reaction proceeds via a sulfinate adduct, which is stable in alkaline solution and can be converted to 1,4-dihydropyridines by protonation of the sulfinate function (Scheme 6).[22] An inexpensive reduction agent, simple experimental conditions and complete regioselectivity for γ-substituted pyridinium salts are advantages of this reduction.[23] The soft nucleophile, dithionite anion, and the reversible character of the first step of reduction, lead regioselectively to the 1,4-dihydro products. Regioselective cyclizations upon activated aromatic rings such as indole can be achieved by acid treatment of 1,4-dihydropyridines, because the iminium salt generates at the β-carbon of the unsubstituted enamine rather than at the vinylogous amide moiety.[6]



Scheme 6. Sodium dithionite reduction of pyridinium salts.

Dithionite reduction of pyridinium salts followed by acid treatment has been widely used in the synthesis of indolo[2,3-α]quinolizidine derivatives.[6,24,25] In the total synthesis of deplancheine (**17**), sodium dithionite reduction of salt **18** was followed by cyclization of enamine **19**, under acidic conditions, to indoloquinolizidine **20**. Only two more steps, acid treatment and reduction, were needed to accomplish the total synthesis of deplancheine **17** (Scheme 7).[26]



Scheme 7. Total synthesis of deplancheine (**17**).[26]

As with the Kröhnke procedure, the need for an electron withdrawing substituent at the β-position in pyridinium salts has been the main disadvantage of the dithionite reduction. However, Wong and his collegues[23] solved this problem with a change of solvent. Instead of aqueous methanol, they used a two-phase solution of toluene and water or diethyl ether and water in the sodium dithionite reduction of pyridinium salts and obtained the corresponding 1,4-dihydropyridines. The dithionite reduction of *N*-methyl pyridinium salt proved unsuccessful despite the two-phase solvent system, but with long-chain *N*-alkyl or *N*-benzyl substituents the recovery of the corresponding 1,4-dihydropyridine was 80% after 10 min at 100°C. Alkyl substituents at positions 3 or 3 and 5 did not affect the yield of the reaction.[23]

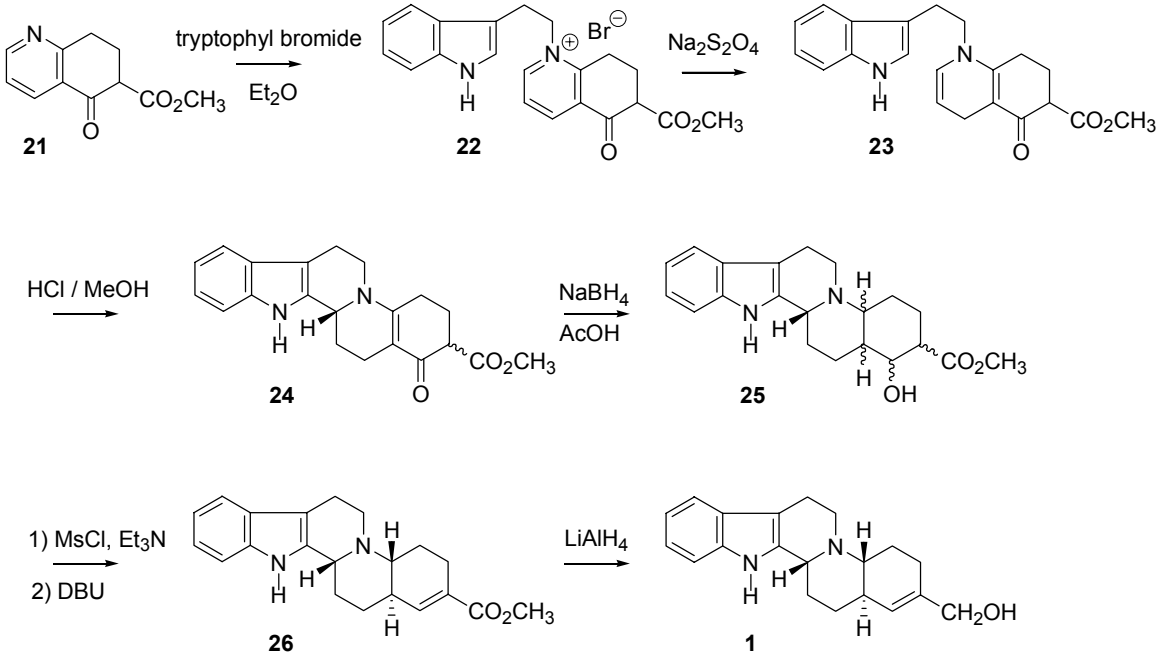
The 1,4-dihydropyridines prepared by sodium dithionite reduction can be converted to 2,6-dicyanopiperidines. More about the synthesis of 2,6-dicyanopiperidines and their applications to alkaloid syntheses will be presented in Section 3.2.2.

2.2.1 Total synthesis of tangutorine

The isolation of the novel indole alkaloid tangutorine (**1**) from the leaves of *Nitraria tangutorum* in 1999 by Duan *et al.*[27] and the promising synthetic strategy for tangutorine skeleton by Berner *et al.*[4] provided the basis for the total synthesis of tangutorine (**1**).[IV,V] So far, this new compound is the only known natural product containing the benz[*f*]indolo[2,3-*α*]quinolizidine unit.

In modification of the synthesis of Berner *et al.*,[4] we first prepared the desired quinoline derivative and attached it to the tryptophyl bromide to afford salt **22**. Since the total yield of the tangutorine skeleton was relatively low due to the different stereoisomers formed in the Fry reaction,[4] we decided to use dithionite reduction instead to avoid epimerization reactions.[IV,V]

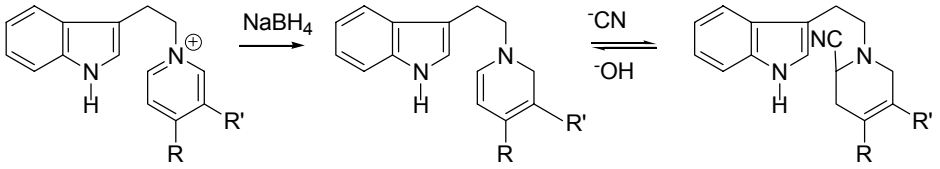
Cyclization of compound **23** in HCl/MeOH to compound **24** and reduction with sodium borohydride in glacial acetic acid overnight yielded a mixture of isomers of compound **25**. The vinylogous amide in compound **24** inhibited the $NaBH_4$ reduction. Tangutorine (**1**) was afforded after dehydration of compound **25** and final reduction of the ester group in compound **26** (Scheme 8).



Scheme 8. Total synthesis of (±)-tangutorine (**1**).[IV,V]

3 Cyano-masked iminium intermediates

In the second part of this work, cyano-masked iminium ions were studied as intermediates for the synthesis of indole alkaloids. The cyanide ion can be used as a protecting group for unstable iminium intermediates. The introduction of cyanide ion to $R_2C{=}NR$ and $R_2C{=}N^+R_2$ bonds to give α-amino nitriles has been demonstrated in a large number of cases. Fry[28] and Fry and Beisler[29] for example have shown that this reaction allows the preparation of protected 1,2-dihydropyridines (Scheme 9). These α-aminonitriles also retain their reactivity for nucleophilic addition.[2] The method can be adapted for iminium intermediates of other dihydropyridines, too.

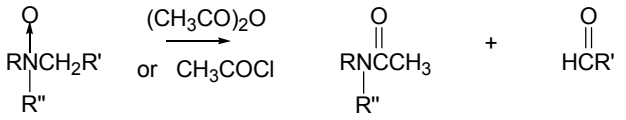


Scheme 9. An example of the Fry reaction.

3.1 Polonovski–Potier reaction

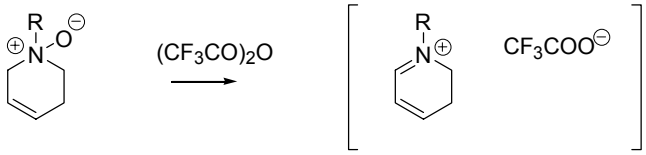
In place of 1,4-dihydropyridines 5,6-dihydropyridinium derivatives can be used as intermediates for substituting the γ-position of the pyridinium ring. 5,6-Dihydropyridinium intermediates are valuable synthons for the preparation of functionalized piperidines, as one can envisage successive control over three carbon centres (C-2,3,4).[2] These 5,6-dihydropyridinium intermediates can be obtained by the Polonovski-Potier reaction.[30–33]

The original Polonovski reaction[34] involves the treatment of a tertiary amine *N*-oxide with acetic anhydride or acetyl chloride, resulting in rearrangement to the *N*-acetyl derivative of the corresponding secondary amine and aldehyde (Scheme 10). This reaction was first looked upon as a means of effecting *N*-demethylation of tertiary amines. However, the central feature of the Polonovski reaction is the transformation of an *N*-oxide to an iminium ion intermediate. This can occur through loss of an α-hydrogen or through fragmentation of an α-carbon bond.[35]



Scheme 10. The Polonovski reaction.[35]

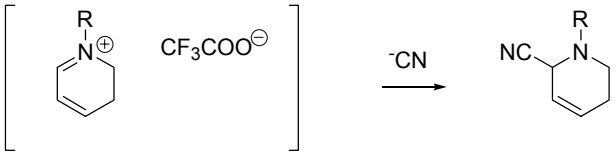
The Polonovski reaction can be modified by replacing acetic anhydride with trifluoroacetic anhydride. In this case the reaction can be stopped at the iminium ion stage, and the reaction of *N*-alkyl-1,2,5,6-tetrahydropyridine *N*-oxides leads to the regiospecific formation of 5,6-dihydropyridinium salt intermediates in high yields (Scheme 11). This is called the modified Polonovski or the Polonovski-Potier reaction.[30,32]



Scheme 11. The Polonovski–Potier reaction.

3.1.1 Cyano-trapping method

In face of the instability of 5,6-dihydropyridinium salts, Grierson *et al.*[2] developed more stable iminium ion equivalents by nucleophilic addition of cyanide ion to 5,6-dihydropyridinium salts. This cyano-trapping method (Scheme 12) led to 2-cyano-1,2,5,6-tetrahydropyridine products, which are stable versatile synthetic intermediates and can be considered synthetic equivalents of the corresponding iminium ion species.[2,21]



Scheme 12. Husson's cyano-trapping method.

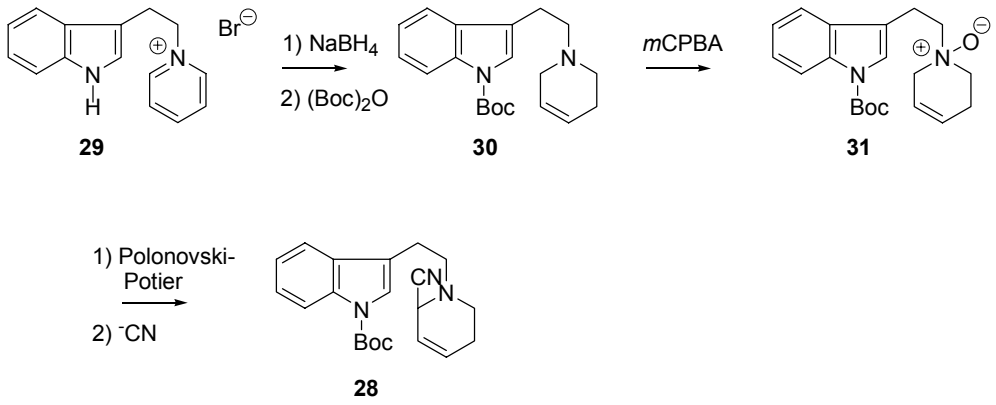
The application of this method to the synthesis of indole alkaloids could be achieved by using 1'-[2-(3-indolyl)ethyl]-1',2',5',6'-tetrahydropyridine *N*-oxides. However, it was anticipated that unwanted cleavage of the C_5–C_6 bond or intramolecular cyclization could

occur during reaction of *N*-oxides with trifluoroacetic anhydride (the Polonovski–Potier reaction), leading to the formation of a multitude of products. As both of these problems originate from the donating ability of the indole nitrogen lone pair, deactivation of the indole nitrogen was necessary. This deactivation problem was solved by protecting the nitrogen with a phenylsulfonyl group.[36,37]

However, the removal of the *N*-benzenesulfonyl group introduced an additional step into the syntheses at a point that required the isolation of fragile intermediates. Through the replacement of benzenesulfonyl group with *t*-butyloxycarbonyl (Boc), a better overall yield was achieved. Boc is sufficiently electron withdrawing to prevent side reactions during aminonitrile formation and does not interfere with the condensation step. It is acid labile, being readily cleaved by treatment with acid at room temperature so that it is possible to carry out cyclization and deprotection in the same operation.[36]

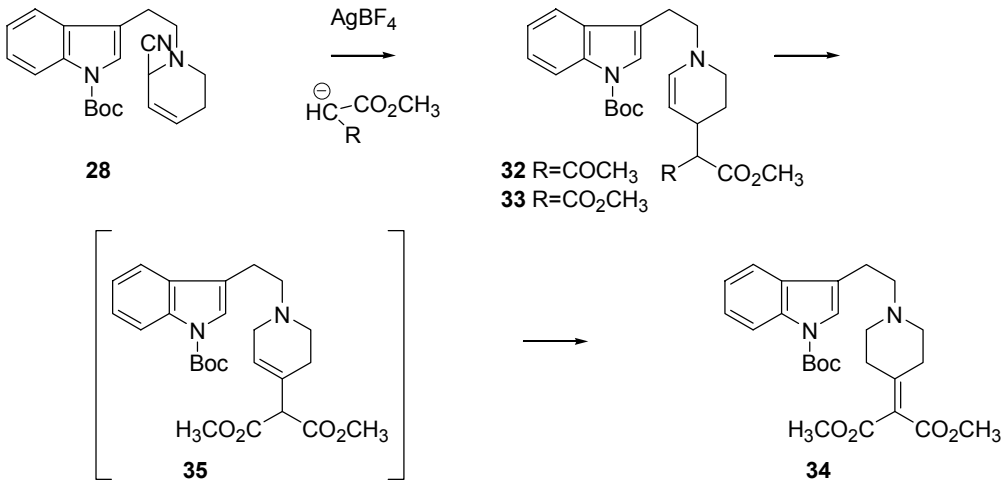
3.1.2 Preparation of antirhine synthon

The cyano-trapping method[36] was applied in the preparation of the indolo[2,3-α]quinolizidine derivative **27**, a possible antirhine (**2**) synthon.[II] The preparation of the 1'-[2-(3-indolyl)ethyl]-2'-cyano-1',2',5',6'-tetrahydropyridine (**28**) starting from salt **29** was successful: The sodium borohydride reduction and Boc protection of indolyl nitrogen was followed by oxidation of compound **30** affording *N*-oxide **31**. The Polonovski–Potier reaction and additional cyano-trapping of the formed 5,6-dihydropyridinium salt afforded compound **28**, as expected (Scheme 13).



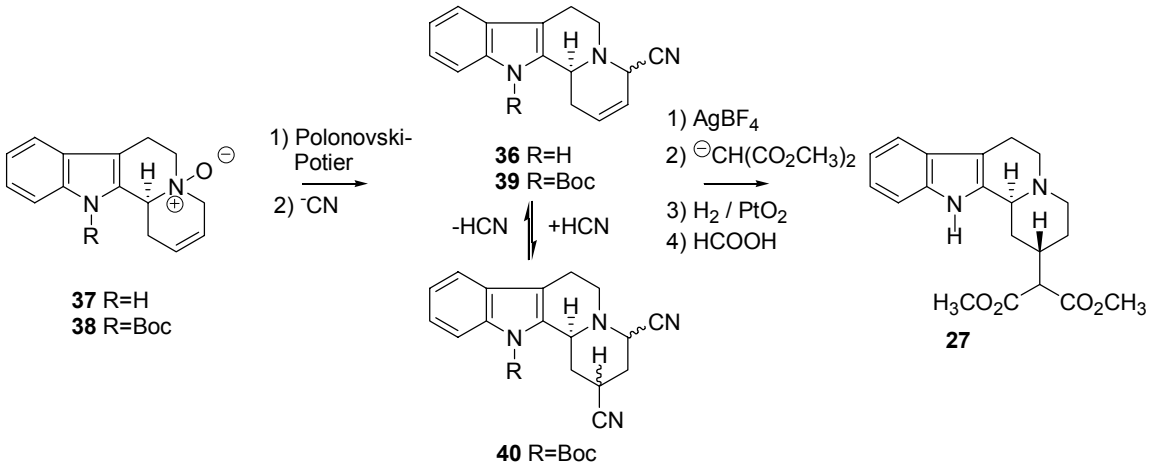
Scheme 13. Preparation of the 1'-[2-(3-indolyl)ethyl]-2'-cyano-1',2',5',6'-tetrahydropyridine (**28**) via the Polonovski–Potier reaction and cyano-trapping.[II]

Reaction of compound **28** with sodium methyl acetoacetate or with exactly the same anion as used by Grierson *et al.*,[36] sodium dimethyl malonate, in the presence of silver tetrafluoroborate ($AgBF_4$) did not yield the expected 1',2',3',4'-tetrahydropyridine **32** or **33**, respectively. The reaction with sodium methyl acetoacetate did not proceed at all, and the condensation of compound **28** with sodium dimethyl malonate yielded 58% of piperidine derivative **34**. This result can be explained by the rapid transformation of compound **33** via intermediate **35** to compound **34** (Scheme 14).



Scheme 14. Addition of sodium methyl acetoacetate or sodium dimethyl malonate to compound **28**.[II]

After our failure to obtain the target compound **27** by this method, we decided to test an alternative route to the preparation of antirhine-type indole alkaloids. Instead of condensation of sodium dimethyl malonate with compound **28** we used carbonitrile **36** as synthon. This was obtained by the Polonovski–Potier reaction followed by cyano-trapping from *N*-oxide **37**. The condensation of compound **36** with dimethyl malonate in the presence of $AgBF_4$ followed by catalytic hydrogenation yielded compound **27**, as desired. To improve the overall yield, we prepared a Boc protected intermediate **38**. The Polonovski-Potier reaction, followed by cyanotrapping, yielded the expected 4-monocyano compound **39**, but as minor product, where 2,4-dicyano compound **40** was the major product (Scheme 15).

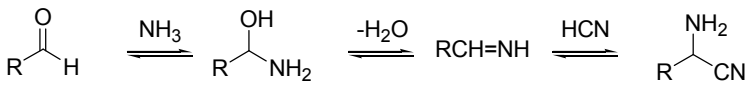


Scheme 15. Alternative route for the synthesis of indolo[2,3-α]quinolizidine derivative **27**.[II]

To avoid unwanted reactions during the purification,[II] the crude product of cyano-trapping consisting of compounds **39** and **40** was treated with $AgBF_4$ and then with sodium dimethyl malonate. Catalytic hydrogenation followed by deprotection in acidic conditions gave compound **27**. Despite difficulties in the Polonovski–Potier reaction, the overall yield was improved by using Boc-protected intermediate **38**.

3.2 2,6-Dicyanopiperidines

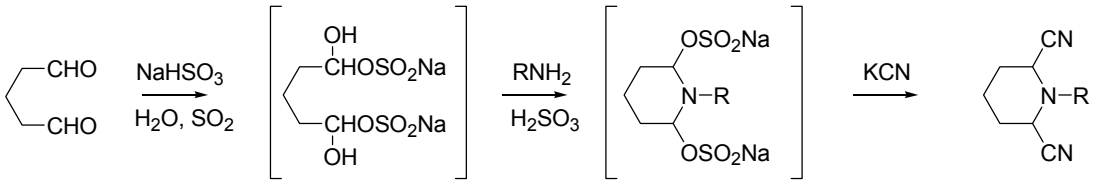
N-substituted 2,6-dicyanopiperidines are versatile synthetic intermediates in the preparation of various pharmacologically important piperidine alkaloids.[38,39] 2,6-Dicyanopiperidines have commonly been prepared by a modification of the Strecker reaction,[40] i.e., condensation of glutaraldehyde or its equivalents with primary amines in the presence of cyanide ion (Scheme 16).[41] However, as in the syntheses of Fry,[28] Fry and Beisler[29] and Grierson *et al.*,[2] the reaction of cyanide ions with iminium ions can also be applied to the preparation of 2,6-dicyanopiperidines.



Scheme 16. The Strecker reaction.

3.2.1 Modification of the Strecker reaction

Henry[41] reported in 1959 the formation of 2,6-dicyanopiperidine instead of 1,5-diamino-1,5-dicyanopentane in the reaction of glutaraldehyde and ammonium cyanide. A few years later Johnson and Crosby[42] described reactions of the dicyanohydrins of glutaraldehyde and 3-methylglutaraldehyde with aliphatic amines. The yields of *N*-alkyl-2,6-dicyanopiperidines ranged from 50% in the case of ammonia to 90% for more bulky amines. The similar 1-amino-2,6-dicyanopiperidine was obtained after reaction of glutaraldehyde with hydrazine and hydrogen cyanide. Later, several variations were reported for the preparation of 2,6-dicyanopiperidines by condensation of glutaraldehyde with amines in the presence of cyanide ion.[43,44] Takahashi *et al.*[45] have also used this Strecker-type reaction of glutaraldehyde with aryl- and benzylamines. The condensation of glutaraldehyde with aniline, *p*-anisidine and benzylamine using sodium hydrogen sulfite and sulfurous acid gave the corresponding dicyanopiperidines in 74%, 86% and 67% yields, respectively (Scheme 17).

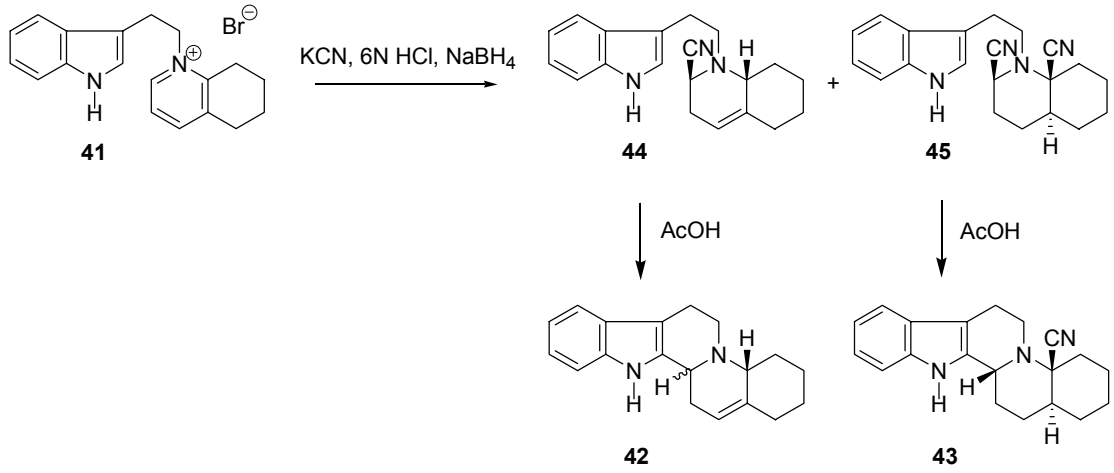


Scheme 17. Preparation of 2,6-dicyanopiperidines by Takahashi *et al*.[45]

Although the yields of Strecker-type reactions are high, glutaraldehydes have a tendency to polymerize and substituted glutaraldehydes are of limited availability. A different approach to synthesis of analogous substituted *N*-alkyl-2,6-dicyanopiperidines was thus of interest.[III]

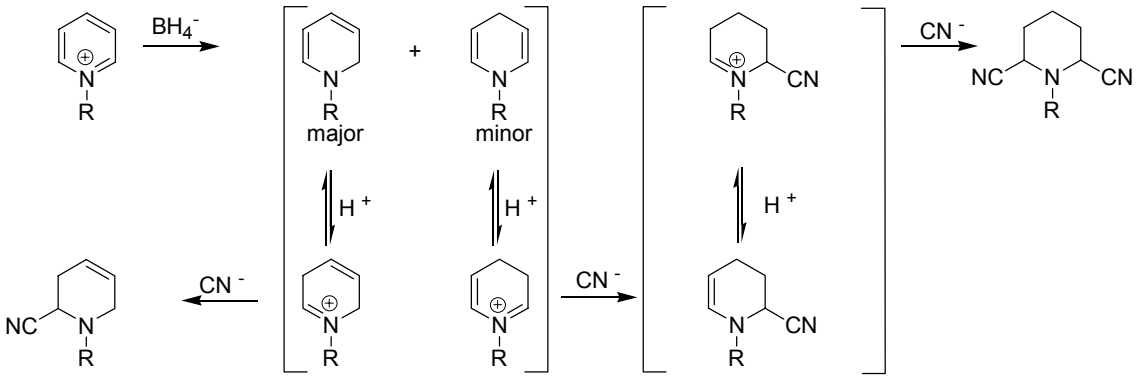
3.2.2 New synthetic pathway to 2,6-dicyanopiperidines

In the synthesis of tangutorine skeleton by Berner *et al.*[4] the Fry reaction of salt **41** followed by acid treatment yielded, in addition to the expected isomeric mixture **42**, the unexpected α-amino nitrile **43**. It is commonly accepted that only monocyanated products are formed in the Fry reaction. However, the isolation of intermediates **44** and **45** confirmed the formation of substituted dicyano derivatives as well (Scheme 18).[III]



Scheme 18. Formation of dicyano intermediate **45** in the Fry reaction of salt **41**.[III]

The presence of dicyano compounds in the Fry reaction can be explained by the known mechanism for sodium borohydride reduction of pyridinium and related salts.[46] In addition to the 1,2-dihydropyridines, minor amounts of 1,4-dihydropyridine intermediates are formed. Under acidic conditions, 1,2-dihydropyridine is protonated to give an iminium ion, which reacts with a cyanide ion, leading to *N*-alkyl-2-cyano-1,2,3,6-tetrahydropyridine. Similarly, 1,4-dihydropyridine is protonated and reacts with cyanide. This is followed by a second protonation, leading to 2,6-dicyanopiperidine (Scheme 19).[III]



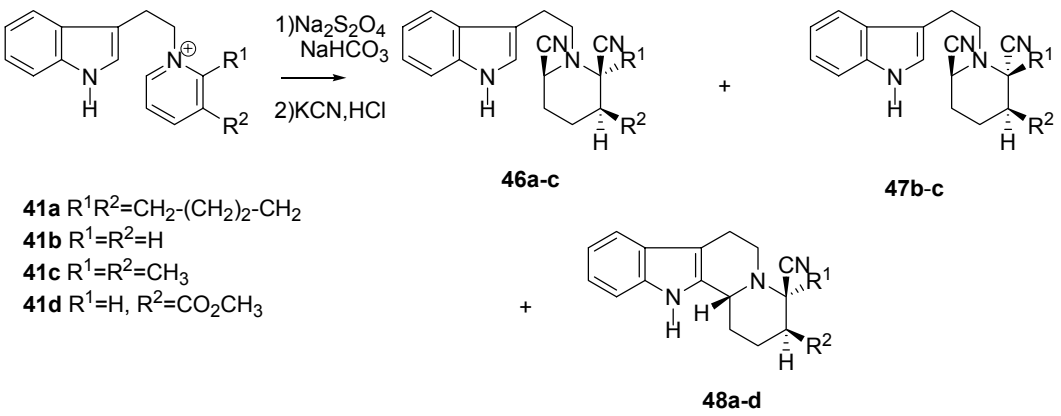
Scheme 19. The mechanism for sodium borohydride reduction of pyridinium salts followed by addition of cyanide ion.[III]

As described earlier, sodium dithionite reduction of pyridinium salts affords the corresponding 1,4-dihydropyridines. The addition of potassium cyanide under acidic conditions enables an easy access to 2,6-dicyano piperidines (Scheme 19).

We chose[III] four pyridinium salts to study the formation of 2,6-dicyanopiperidines under the Fry reaction conditions with use of sodium dithionite as reductant. These were 1'-[2-(3-indolyl)ethyl]-5',6',7',8'-tetrahydroquinolinium bromide (**41a**), 1'-[2-(3-indolyl)ethyl]-pyridinium bromide (**41b**), 2',3'-dimethyl-1'-[2-(3-indolyl)ethyl]pyridinium bromide (**41c**) and (3'-methoxycarbonyl-1'-[2-(3-indolyl)ethyl]pyridinium bromide (**41d**).

When salts **41a**–**d** were subjected to the Fry reaction conditions (KCN, HCl, $NaBH_4$), the 2,6-dicyano compound (**46a**, **47b**, **47c**) was found and isolated in every reaction except that of salt **41d**, where the ester group stabilizes more the 1,2- than the 1,4-dihydropyridine intermediate. The expected monocyano compound was also present.[III]

2,6-dicyano compounds were also obtained when the reduction of salts **41a**–**c** with sodium dithionite was followed by the addition of potassium cyanide under acidic conditions. In the reaction of salt **41a** one dicyano product **46a** was formed. In the reaction of salts **41b** and **41c** two different 2,6-dicyano compounds were formed (**46b**, **47b** and **46c**, **47c**, respectively) (Scheme 20).



Scheme 20. Sodium dithionite reduction of salts **41a**–**d** followed by addition of cyanide.

In the reduction of salt **41d**, only the cyclized monocyano compound **48d** was formed. Because of the stabilizing ester group, the 1,4-dihydropyridine intermediate is more stable in this reaction than with salts **41a**–**c**. Under acidic conditions, the nucleophilic attack by the indole is faster than the addition of a cyanide ion to C-6, and the cyclized monocyano product **48d** is formed. The cyclized monocyano compound **48a**–**c** was also formed in the reaction of salts **41a**–**c**.

3.2.3 Stereochemistry of 2,6-dicyanopiperidines

Considering the equilibrating conditions under which the dicyano compounds are formed in the Strecker–type reaction, Johnson and Crosby[42] concluded that these compounds exist in the more stable *cis*-configuration where both nitrile groups are equatorial (Figure 3). It has been shown, however, that the diaxial conformation is preferred.[47,48] In this conformation the molecules can benefit from the stabilizing anomeric effects between the nitrogen lone pair of electrons and the anti-periplanar nitrile groups.

Takahashi *et al.*[45] and Bonin *et al.*[47] have studied the stereochemistry of dicyano compounds formed in these glutaraldehyde reactions. They found that heating diaxial 1-benzyl- or 1-(*p*-methoxyphenyl)-1,6-dicyanopiperidine in ethanol for 40-48 hours gave rise to a new stereoisomeric product. NMR spectrometric data showed this new product to have the cyano groups in *trans*-configuration. Bonin *et al.*[47] showed that the molecule exists as an equilibrium mixture of conformers where one of the cyano groups is in axial and the other in equatorial position. The NMR values were an average of axial and equatorial

hydrogens. The same results were obtained in studies of 1-amino-2,6-dicyanopiperidine when the diaxial isomer was heated in ethanol for 5 hours.[48]

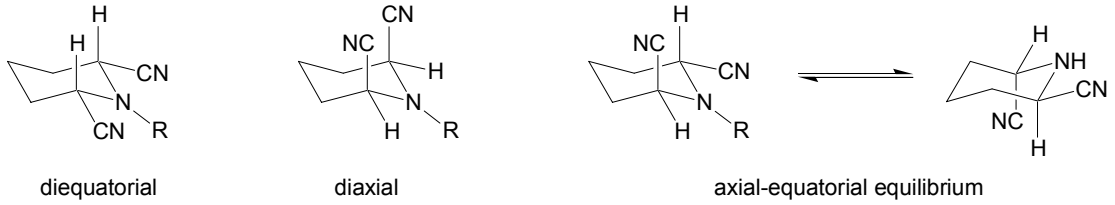


Figure 3. Stereochemistry of 2,6-dicyanopiperidines.

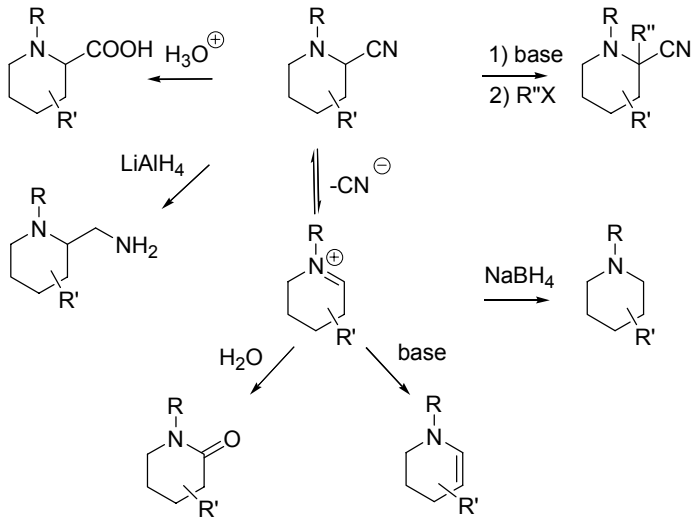
In our studies,[III] the $Na_2S_2O_4$/KCN reaction resulted mainly in two different sets of dicyano products. The main products **46a**–**c** had the cyano groups in preferred diaxial conformation. The minor products **47b** and **47c** had the cyano groups in *trans*-conformation, and the NMR spectrometric data confirmed the results of Bonin *et al.*[47] showing that the molecules exist as an equilibrium mixture of conformers (Figure 3) and that the values determined were an average of axial and equatorial hydrogens.

The stereochemistry of the dicyano products in the Fry reaction differed from the stereochemistry found with other methods. The main dicyano products starting from salts **41b** and **41c** had the axial-equatorial *trans* conformation. However, in the Fry reaction of the tetrahydroquinolium salt **41a** the dicyano product was the compound **46a** with cyanides in diaxial conformation.[III]

The dissimilar reaction temperatures could be one reason for the stereochemically different products in the Fry and the $Na_2S_2O_4$/KCN reactions. Most likely, the axial-equatorial dicyano compounds **47b** and **47c** were due to the kinetically controlled addition of cyanide, whereas the diaxial dicyano compounds **46a**–**c** were formed under thermodynamic conditions. The difference between salts **41a** and **41b**–**c** in the Fry reaction can be explained by the preferred *trans* ring juncture in compound **46a**, which forces the C-8a cyano group to axial position.

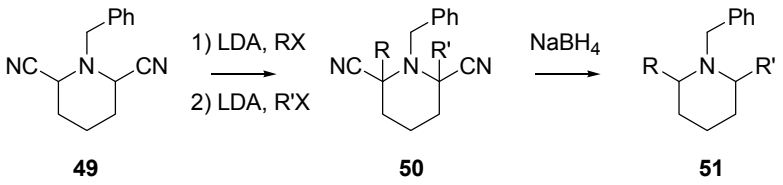
3.2.4 Synthetic applications

The reactivity of nitriles paves the way to a wide variety of substituted piperidines (Scheme 21).



Scheme 21. Reactivity of α-amino nitriles.

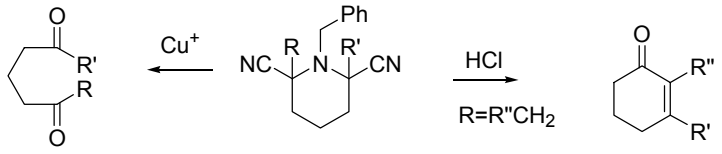
Only a few methods have been adapted for dicyano compounds. Takahashi *et al.*[38] have developed a synthetic method for the preparation of unsymmetrical 2,6-dialkylpiperidines. The reaction of 1-benzyl- or 1-phenyl-2,6-dicyanopiperidine with various alkyl halides gave 2-alkyl- and 2,6-dialkyl- (either 1-benzyl- or 1-phenyl-) 2,6-dicyanopiperidines in high yields. With *N*-phenyl substituted dicyanopiperidine, the alkylation gave symmetrical dialkylated products. However, selectively monoalkylated products were formed in the alkylation of *N*-benzyl substituted compound **49**. The second alkylation with different alkyl halides led to the formation of unsymmetrical 2,6-dialkyl 2,6-dicyanopiperidines **50**. The corresponding decyanated products **51** were formed upon treatment of alkylated products with sodium borohydride at 70°C (Scheme 22). The yields for alkylations were very good: for monoalkylated products 82–90% and for dialkylated 71–99%. The best yields were obtained when one alkyl substituent was small and the other a longer polymethylene chain. This selective method is important for the preparation of unsymmetrical dialkylated piperidines such as solenopsin A (*trans*-2-methyl-6-*n*-undecylpiperidine).[38]



49 **50** **51**

Scheme 22. Alkylation of 1-benzyl-2,6-dicyanopiperidines.[38]

2,6-Dialkyl-2,6-dicyanopiperidines can also be converted to substituted α,β-unsaturated cyclohexenones **52** by hydrolysis in an aqueous solution of hydrochloric acid. When the hydrolysis is carried out in an aqueous solution of cupric sulfate or acetate, δ-diketones **53** can be obtained in good yields (Scheme 23).[45,49]



53 **50** **52**

Scheme 23. Preparation of α,β-unsaturated cyclohexenones **52** and δ-diketones **53**.[45,49]

4 Conclusions

The synthesis of indole alkaloids via 1,4-dihydropyridine stage was studied and methods taking advantage of cyano-masked iminium ions were explored. The addition of nucleophiles to the γ-position of 1'-[2-(3-indolyl)ethyl]pyridinium salts allowed a short synthetic route to indole alkaloid precursors. 1,4-Dihydropyridines were formed in both the Kröhnke procedure and sodium dithionite reduction. Their instability is a major problem when there is no electron withdrawing substituent at the β-position of the pyridinium ring. In this work, it was shown that the Kröhnke procedure can also be used for pyridinium salts without an electron withdrawing substituent at the β-position of the pyridinium ring.[I] Even though the yields were relatively low, the simplicity of the method makes it viable for indole alkaloid synthesis. The dithionite reduction of 1'-[2-(3-indolyl)-ethyl]-6'-methoxycarbonyl-5'-oxo-5',6',7',8'-tetrahydroquinolinium bromide (**22**) opened a synthetic pathway via 1,4-dihydropyridine intermediate to the total synthesis of the novel indole alkaloid tangutorine (**1**).[IV,V]

The instability of 5,6-dihydropyridines can be solved by the cyano-trapping method. This method was utilised in the synthesis of a potential synthon of antirhine (**2**). The addition of dimethyl malonate to the cyclized compound **36** was a better choice than addition to the open compound **28**.[II]

The formation of 2,6-dicyanopiperidines in the Fry reaction was demostrated with three salts. 1,4-Dihydropyridines were confirmed as the intermediates in this reaction by examining sodium dithionite reduction with the same starting materials.[III] These reactions opened a new pathway to 2,6-dicyanopiperidines, which are very useful in several alkaloid syntheses. This method solves the problem of the limited availability of substituted glutaraldehydes, as variously substituted pyridines can be used in their place. It seems that specific isomeric structures of 2,6-dicyanopiperidines can be prepared through careful adjustment of the reaction temperature.

The methods presented here open synthetic pathways to several indole alkaloids that are shorter routes than the pathways previously used. Further studies to improve the yields of the critical reaction steps need to be carried out to enable the wider application of the methods.

5 References

1. Hesse, M., *Alkaloid Chemistry*, John Wiley & Sons, Inc., New York 1981, p. 11.
2. Grierson, D. S., Harris, M. and Husson, H.-P., *J. Am. Chem. Soc.* **102** (1980) 1064-1082.
3. Le Men, J. and Taylor, W. I., *Experientia* **21** (1965) 508-510.
4. Berner, M., Tolvanen, A. and Jokela, R., *Tetrahedron Lett.* **40** (1999) 7119-7122.
5. Patterson, A. M., Capell, L. T. and Walker, D. F., *The Ring Index*, 2nd Ed, American Chemical Society, New York 1960, p. 36, 168.
6. Bennasar, M.-L., Lavilla, R., Alvarez, M. and Bosch, J., *Heterocycles* **27** (1988) 789-824.
7. Kröhnke, F., *Angew. Chem.* **65** (1953) 605-628.
8. Kröhnke, F., Ellgast, K. and Bertram, E., *Liebigs Ann. Chem.* **600** (1956) 176-210.
9. Ahlbrecht, H. and Kröhnke, F., *Liebigs Ann. Chem.* **704** (1967) 133-139.
10. Mauzerall, D. and Westheimer, F. H., *J. Am. Chem. Soc.* **77** (1955) 2261-2264.
11. Hutton, R. F. and Westheimer, F. H., *Tetrahedron* **3** (1958) 73-77.
12. Minato, H., Fujie, S., Okuma, K. and Kobayashi, M., *Chem. Lett.* **1977** 1091-1094.
13. Bosch, J. and Bennasar, M.-L., *Synlett* **1995** 587-596.
14. Lounasmaa, M. and Jokela, R., *Tetrahedron Lett.* **27** (1986) 2043-2044.
15. Lounasmaa, M. and Koskinen, A., *Tetrahedron Lett.* **23** (1982) 349-352.
16. Wenkert, E., *Pure Appl. Chem.* **53** (1981) 1271-1276.
17. Wenkert, E., Chang, C.-J., Chawla, H. P. S., Cochran, D. W., Hagaman, E. W., King, J. C. and Orito, K., *J. Am. Chem. Soc.* **98** (1976) 3645-3655.
18. Wenkert, E. and Reynolds, G. D., *Synth. Commun.* **3** (1973) 241-243.
19. Jokela, R., Taipale, T., Ala-Kaila, K. and Lounasmaa, M., *Heterocycles* **24** (1986) 2265-2271.
20. Lounasmaa, M. and Jokela, R., *Heterocycles* **31** (1990) 1351-1358.
21. Lounasmaa, M., *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, vol. 1, Elsevier, Amsterdam 1988, pp. 189-122.
22. Blankenhorn, G. and Moore, E. G., *J. Am. Chem. Soc.* **102** (1980) 1092-1098.
23. Wong, Y.-S., Marazano, C., Gnecco, D. and Das, B. C., *Tetrahedron Lett.* **35** (1994) 707-710.

24. Supple, J. H., Nelson, D. A. and Lyle, R. E., *Tetrahedron Lett.* **1963** 1645-1649.
25. Jokela, R., Miettinen, J. and Lounasmaa, M., *Heterocycles* **32** (1991) 511-520.
26. Besselièvre, R., Cosson, H.-P., Das, B. C. and Husson, H.-P., *Tetrahedron Lett.* **21** (1980) 63-66.
27. Duan, J.-A., Williams, I. D., Che, C.-T., Zhou, R.-H. and Zhao, S.-X., *Tetrahedron Lett.* **40** (1999) 2593-2596.
28. Fry, E. M., *J. Org. Chem.* **29** (1964) 1647-1650.
29. Fry, E .M. and Beisler, J. A., *J. Org. Chem.* **35** (1970) 2809-2811.
30. Cavé, A., Kan-Fan, C., Potier, P. and Le Men, J., *Tetrahedron* **23** (1967) 4681-4689.
31. Ahond, A., Cavé, A., Kan-Fan, C., Husson, H.-P., de Rostolan, J. and Potier, P., *J. Am. Chem. Soc.* **90** (1968) 5622-5623.
32. Potier, P. *Rev. Latinoamer. Quim.* **9** (1978) 47-54.
33. Ahond, A., Cavé, A., Kan-Fan, C., Langlois, Y. and Potier, P., *J. Chem. Soc. Chem. Commun.* **1972** 517-518.
34. Polonovski, M. and Polonovski, M., *Bull. Soc. Chim. Fr.* **41** (1927) 1190-1208.
35. Grierson, D. S., *Organic Reactions* **39** (1991) 85-295.
36. Grierson, D. S., Harris, M. and Husson, H.-P., *Tetrahedron* **39** (1983) 3683-3694.
37. Grierson, D. S., Vuilhorgne, M., Husson, H.-P. and Lemoine, G., *J. Org. Chem*. **47** (1982) 4439-4452.
38. Takahashi, K., Kurita, H., Ogura, K. and Iida, H., *J. Org. Chem.* **50** (1985) 4368-4371.
39. Braekman, J. C. and Daloze, D., *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, vol 6, Elsevier, Amsterdam 1990, pp. 421-466.
40. Strecker, A., *Liebigs Ann. Chem.* **75** (1850) 27-51.
41. Henry, R. A., *J. Org. Chem.* **24** (1959) 1363-1364.
42. Johnson, H. E. and Crosby, D. G., *J. Org. Chem.* **27** (1962) 1298-1301.
43. Dold, O., *Chem. Ber.* **96** (1963) 2052-2056.
44. Roy, R. B. and Karel, M., *Can. J. Biochem.* **51** (1973) 942-943.
45. Takahashi, K., Mikajiri, T., Kurita, H., Ogura, K. and Iida, H., *J. Org. Chem.* **50** (1985) 4372-4375.
46. Joule, J. A. and Smith, G. F., *Heterocyclic Chemistry*, Van Nostrand Reinhold, London 1972, p. 68.

47. Bonin, M., Chiaroni, A., Riche, C., Beloeil, J.-C., Grierson, D. S. and Husson, H.-P., *J. Org. Chem.* **52** (1987) 382-385.
48. Takahashi, K., Tachiki, A., Ogura, K. and Iida, H., *Heterocycles* **24** (1986) 2835-2840.
49. Takahashi, K., Asakawa, M. and Ogura, K., *Chem. Lett.* **1988** 1109-1112.

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