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NEW 1-AZABICYCLO[3.2.2]NONANE DERIVATIVES OBTAINED BY NUCLEOPHILIC DISPLACEMENT AT CARBON C9 OF CINCHONA ALKALOIDS

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ABSTRACT. Nucleophilic substitution of mesylates prepared from cinchona alkaloids, generated new 1-azabicyclo[3.2.2]nonan derivatives by cage extension rearrangement reactions which accompanied the displacement of the leaving group. Moderate yields of substituted [3.2.2]azabicyclo derivatives were obtained when water, potassium cyanide or phthalimide nucleophiles were employed. The new substituted [3.2.2]azabicyclo derivatives were further functionalized by oxidation, reduction or condensation reactions.

Keywords: *cinchona alkaloids, SN-displacement, 1-azabicyclo[3.2.2]nonane*

INTRODUCTION

Cinchona alkaloids, isolated from the bark of several species of *cinchona* trees, are the organic molecules with the most colourful biography [1]. Their history dates back to the early seventeenth century when they were first introduced into the European market after the discovery of the antimalarial property of cinchona bark and the subsequent isolation of its active compound, quinine by P.J. Pelletier and J.B. Caverntou in 1820. Since then, cinchona alkaloids, especially quinine, have played a pivotal medicinal role in human society.

The role of cinchona alkaloids in organic chemistry was firmly established with the discovery of their potential as resolving agents by Pasteur in 1853, which ushered an era of racemate resolutions by the crystallization of diastereomeric salts [2]. Cinchona alkaloids are readily

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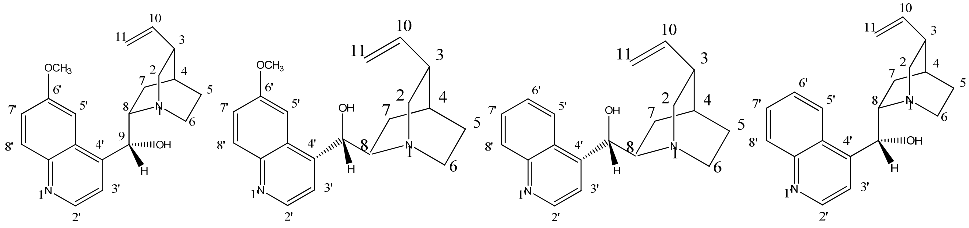
available as pairs of stereoisomers, such as quinine **1** and quinidine **2**, cinchonine **3** and cinchonidine **4** (figure 1).

Since 2000, explosively expanding interest in chiral organocatalysis as a new stream of catalysis has sparked a second renaissance in the use of cinchona alkaloids as organocatalysts. Thus, cinchona alkaloids and their derivatives are classified as the most "privileged organic chirality inducers", efficiently catalyzing nearly all classes of organic reactions in a highly stereoselective fashion [3].



quinine **1** quinidine **2** cinchonine **3** cinchonidine **4**

***Figure 1**. Structural formulae of cinchona alkaloids*

The key feature responsible for cinchona alkaloids successful use is that they possess diverse chiral skeletons and are easily tuneable for different types of reactions. The presence of 1,2-aminoalcohol subunit containing the highly basic and bulky quinuclidine unit which complements the proximal acidic hydroxyl function, is primarily responsible for their use as additives in catalytic asymmetric reactions and for more other remarkable transformations and skeletal shifts [4].

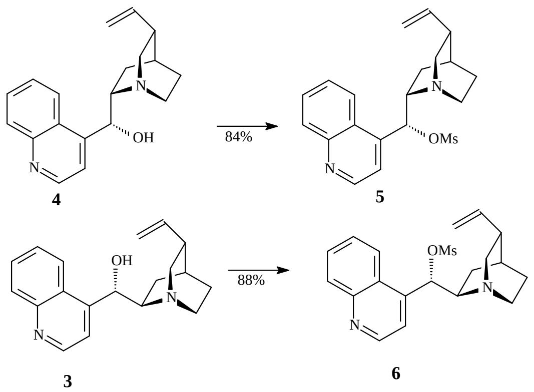
Solvolytic displacements at the saturated carbon are among the best known and the most useful reactions in organic chemistry. Solvolytic displacements at the stereogenic saturated carbon atom linking the two heterocyclic units (C9), of cinchona natural alkaloids, were found to be accompanied by expansion of the 1-azabicyclo[2.2.2]octane structural unit to 1-azabicyclo[3.2.2]nonane, a structural motif which has been scarcely found in nature. A short and simple access to this particular bicyclic system is thus of high interest for exploring its biological and chemical properties. The cage expansion of 1-azabicyclo[2.2.2]octane may occur either *via* a configurationally stable bridgehead iminium ion, or a non classical nitrogen-bridged cation. Ground state conformation, stereoelectronic factors and solvent are crucial features in selecting the reaction conditions [4].

The aim of this work was the study of the nucleophilic displacements at C9 of cinchonine (CD) and cinchonidine (CN) substrates and the formation of 1-azabicyclo[3.2.2]nonane derivatives by cage extension.

RESULTS AND DISCUSSION

In the past, tosylate leaving groups have usually been investigated in solvolysis reactions. Substrates with a neighbouring basic amino function such as cinchona alkaloids gave rise to novel reactivity. Methanolysis of O-tosylated quinine, may appear to be hopelessly complex [1] and after the controversy in the 1960's, C9-functionalized cinchona alkaloids were completely ignored. Hoffmann and co-workers found that a change of the leaving group from tosylate (O-Ts) to methanesulfonate (O-Ms), appears advantageous for many nucleophilic substitutions at C9 and more conveniently, mesylates could be handled more easily [4].

By the reaction of cinchonine (CD) **3** and cinchonidine (CN) **4** substrates with methanesulfonyl chloride under standard conditions [5] we obtained the mesylates CDMs **5** and CNMs **6** respectively (scheme 1), in good yields (76% and 80% respectively).

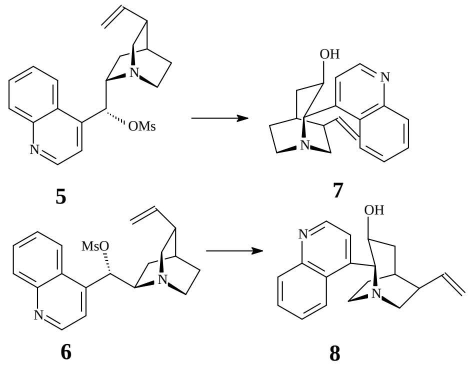


Reagent and conditions: MsCl, NEt_3, THF, rt, 3-16 h

Scheme 1.

Hoffmann and co workers studied the hydrolysis of activated CDMs **5** and CNMs **6** [4]. They observed that CNMs **6** first melt, then dissolve and hydrolyze upon heating in water. After refluxing in pure water the [2.2.2]azabicyclic unit of the substrate is expanded to the [3.2.2]azabicycle product **7** (scheme 2). The hydrolysis of the mesylates can be considered as a green chemistry procedure, since reagents are inexpensive, biodegradable and toxicologically harmless [4,6].

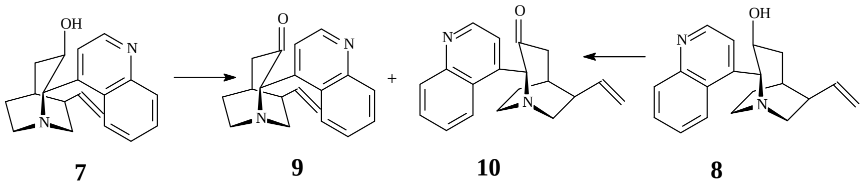
The 1-azabicyclo[3.2.2]nonan derivative **8** was obtained in 52% yields starting with the prepared CNMs **6** (scheme 2).



Reagent and condition:H_2O, reflux, 4-5 h

Scheme 2.

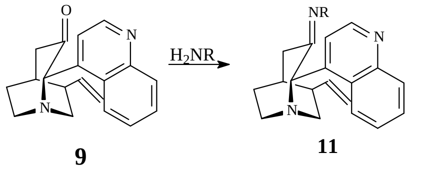
The reaction of dimethylsulfoxide (DMSO) with electrophilic activators has been proven as highly useful in the mild oxidation of alcohols to carbonyls [7]. Swern oxidation of β-aminoalcohol **7** gave not only the expected azabicyclic α-aminoketone **9** but also its epimer **10,** in 2:1 ratio (scheme 3).



Reagent and condition:CH_2Cl_2, DMSO, $(COCl)_2$, NEt_3, -78 - rt

Scheme 3.

Nitrogen containing compounds such as amine, hydroxylamine, hydrazine gave condensation reactions with ketone **9** (scheme 4).

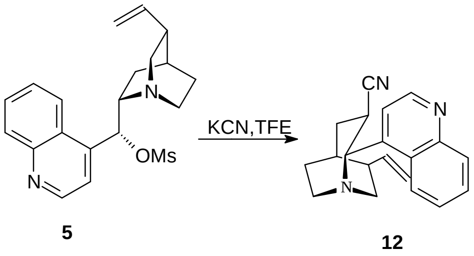


R = H, OH, NH_2 alkyl,

Scheme 4.

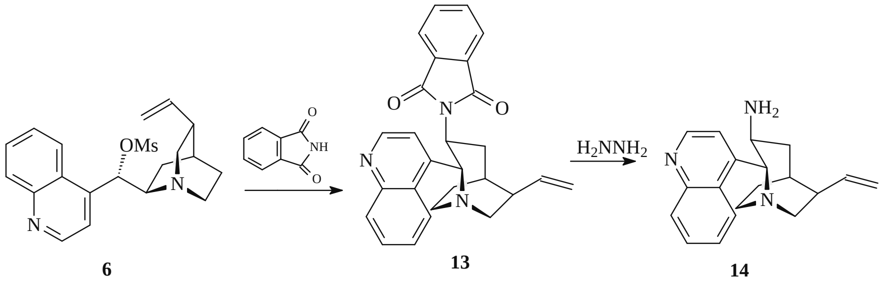
Numerous functional group transformations made the oximes very important intermediates in synthetic chemistry. The classical preparation method implies the reaction of carbonyl compounds with hydroxylamine hydrochloride, in the presence of sodium hydroxide. This method afforded 38% yields of the oxime derived from carbonyl derivative **10**. The IR spectroscopic analysis of oxime **11** has confirmed the presence of characteristic bands due to stretching vibrations of functional groups such as N=C, N-O and O-H.

The synthesis of some other new compounds is based on the nucleophilic substitution previously described as ”second cage expansion” rearrangement reaction, which proceed *via* a nitrogen-bridged cation intermediary. The second cage expansion is open to many synthetic variations and has been carried out in the presence of different nucleophiles under SN1-like conditions and thus, compounds with practical use in the preparation of drugs and additives for asymmetric synthesis were conveniently prepared [8]. In scheme 5 is presented the preparation of nitrile **12** starting with CDMs **5** and KCN.



Scheme 5.

In 1972, Mitsunobu described the formation of amino-derivatives, by nucleophilic substitution of an alcohol substrate with phtalimide, followed by reduction of the intermediate with hydrazine [9]. The new 3-amino-1-azabicyclo[3.2.2]nonane **14** was obtained in 53% yields by a similar procedure, starting with CNMs **6**. Nucleophilic substitution of -OMs group generated the rearrangement product **13** which was successfully reduced with hydrazine (scheme 6).



Scheme 6.

Further biological investigations are required in order to establish the potential of the new [3.2.2]azabicyclo derivatives **8, 9, 11, 12, 14** as building blocks in the development of new and effective medicinal products.

CONCLUSIONS

Solvolytic displacement of cinchonine mesylate, accompanied by rearrangement reaction generated the new 3-hydroxi-1-azabicyclo[3.2.2]nonan derivative. Other nuclephiles such as cyanide and phtalimide also produced 3-substituted [3.2.2]azabicyclo derivatives by similar cage extension reactions. Optimal experimental procedures for oxidation, condensation or reduction of the new 1-azabicyclo[3.2.2]nonan derivatives were selected.

EXPERIMENTAL SECTION

General. Preparative column chromatography was performed on J.T. Baker silica gel (particle size 30-60 mm), analytical TLC was carried out on aluminium-backed 0,2 mm silica gel 60 F_{254} plates(E. Merck). H-NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated chloroform unless otherwise stated, with TMS as internal standard.

9-O-Mesyl-cinchonine (6).

Cinchonine **3** (40 g, 0,136 mmol) was allowed to react according to the general procedure [4] to afford the corresponding mesily derivatives (38.8 g; η = 76%);H-NMR (400 Hz, $CDCl_3$): δ 8,95(d, J=4,5 Hz, H-2'); 8,21-8,11(m, H-8’, H-5’); 7,79-7,72(m, H-7’); 7,67-7,60(m, H-6’); 7,54-7,47 (bl, H-3’); 6,37 – 6,15 (bl, H-9); 6,03 (dd, J=7,4 ,10,5 Hz, H-10); 5,18-5,08 (m, H-11); 3,45-3,29(m, H-8); 2,91-2,83(m,H-2,H-6); 2,72-2,60 (m, H-2, H-6, H-12,)Ms); 2,31-2,20(m, H-3); 2,01-1,91 (m,H-7); 1,90-1,84 (m, H-4); 1,83-1,68(m, H-7); 1,60-1,55(m, H-5) $C_{20}H_{24}N_2O_3S$(376,15): calc. C 64,92%, H 6,38%, N 7,44%; found C 65,14%, H 6,41%, N7,32%.

2-Quinolin-4-yl-6-vinyl-1-aza-biciclo[3.2.2]nonan-3-ol (8).

O-mesilyl cinchonine **6** (10 g, 0,0268 mmol) and 100 ml water was refluxed for 4 hours.To the reaction mixture was added 10 ml $NaHCO_3$ and pH was adjusted to 12 with NaOH solution. The reaction mixture was diluted with DCM and the organic layer was washed with sat. aq. $NaHCO_3$ and dried (Na_2SO_4). After removal of the solvent the crude product was purified by chromatography (MTBE:MeOH, 9:1), thus obtaining 4,1 g product (η=52%), H-NMR: (400 MHz, $CDCl_3$) δ8,84(d, J=4,5 Hz, H-2'); 8,10-8,05(m, H-8',H-5'); 7,69-7,63 (m,H-7'); 7,60-7,54(m,H-6'); 7,42(d, J=4,5 Hz, H-3'); 6,03(ddd, J=7,1 9,5,17,3 H-10); 5,18-5,09(m, H-11); 4,75-4,65 (m, H-3); 4,33(d, J=10,1 Hz, H-2); 3,59(dd, J=9,5, 15,1 Hz, H-7); 3,3-3,18(m,H-8); 2,61-2,51(m,H-7); 2,44-2,35(m,H-6); 2,29-2,21(m,H-4); 2,19-2,13(m, H-5); 2,07-2,0(m, H-4); 1,92-1,83(m, H-9). $C_{19}H_{22}N_2O$(294,45): calc. C 77,55%, H 7,48%, N 9,52%; found C 77.65%, H 7,58%, N 9,42%.

2-Quinolin-4-yl-6-vinyl-1-azabicyclo [3.2.2] nonan-3-one (9)

1g(3,4 mmol) compound **7** was oxidized under Swern procedure [7], with oxalyl chloride (0,88 g) and DMSO (0,53g). After the oxidation, saturated $NaHCO_3$ was added, followed by extraction with DCM; the organic layer was washed with sat. aq. $NaHCO_3$ and dried over anh. Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography (PE:MTBE, 1:1) and resulted 0,57 g product (η=57%).H-NMR: (400 MHz, $CDCl_3$): δ 8,68(d, J=4,5, H-2'); 8,09-8,02(m,H-8'); 7,82-7,76(m,H-5'); 7,62-7,56(m, H-7'); 7,44-7,32(m,H-6'); 7,05(d, J=4,5, H-3'); 5,74(ddd, J=6,8, 9,8, 17,1, H-10); 4,97-5,03(m, H-11,H-11); 4,02-3,8(m, H-5,OH); 2,37-2,22(m,H-7); 2,29-2,19(m, H-8); 2,17(m, H-6); 1,74-1,89(m,H-9); 1,59-1,34(m,H-2).$C_{19}H_{20}N_2O$(292,36): calc. C 78,05%, H 6,89%, N 9,58%; found C 77,87%, H 7,03%, N 9,42%.

2-Quinolin-4-yl-6-vinyl-1-azabicyclo[3.2.2]nonan-3-oxime (11).

The reaction was conducted with 0,2 g(o,6 mmol) ketone(**9**), hydroxylamine hydrochloride 0,65g(0,03 mmol) in ethanol and solid NaOH. The reaction mixture was refluxed for 1 hour and then cooled to rt. The reaction mixture was diluted with HCl solution. The crystaline product formed was filtered and dried. The product was disolved in DCM purified by column chromatography (MTBE:MeOH, 3:1) and resulted 0,07 g product (η=38%).H-NMR: (400 MHz, $CDCl_3$): δ 8,92(d, J=4,6, H-2'); 8,65(d, J=8,2, H-5'); 8,05(d, J=8,2, H-8');7,66-7,58(m, H-7');7, 44(m, H-6'); 7,31(d, J=4,5 H-3'); 5,92(ddd, J=6,8, 10,5, 17,2, H-10); 5,26-5,17(m,H-11); 4,42(d, J=9,4, 14,3, H=7); 3,9(m,H-2); 3,37-3,27(m, H-7); 2,96-2,81(m,H-8); 2,53-2,43(m, H-8, H-4); 2,31-2,23(m, H-6); 2,11-2,04(m, H4,H5); 2,02-1,92(m, H-9).$C_{19}H_{21}N_3O$(307,38): calc. C 74,23%, H 6,88%, N 13,67%; found C 73,97%, H 6,96%, N 13,48%.

2-Quinolin-4-yl-6-vinyl-1-aza-biciclo[3.2.2]nonan-3-carbonitryl. (12)

O-mesilylcinchonine **6** (1 g, 0,0026 mmol) and 13 ml TFE and KCN(0,52g; 0,008 mmol) was refluxed for 3 days. The reaction mixture was washed with sat. aq. $NaHCO_3$ and dried (Na_2SO_4). After removal of the solvent the crude product was purified by chromatography (ether:MeOH, 9:1) and result 0,37 g product (η=47%). H-NMR: (400 MHz, $CDCl_3$): δ 8,93(d, J=4,5 Hz, H-8'); 8,15(d, J=8,4 Hz, H-8'); 8,01(d, J=8,4 Hz, H-5'); 7,76-7,71(m, H-7'); 7,65-7,59(m, H-6'); 7,39(d, J=4,6 Hz, H-3'); 5,97(m, H-10); 5,28-5,14(m, H-11); 4,80(d, J=11,7 Hz, H-2); 3,60-3,519M, H-3); 3,50-3,40(m, H-80; 3,23-3,13(m, H-8); 2,93-2,84(m, H-7,H-4); 2,56-2,44(m, H-6); 2,30-2,24(m, H-5); 2,11-1,85(m, H-4, H-9).$C_{20}H_{21}N_3$(303,38): calc. C 79,17%, H 6,97%, N 13,85%; found C 79,28%, H 7,09%, N 13,62%.

2-(2-Quinolin-4-yl)-6-vinyl-1-aza-biciclo[3.2.2]nonan-3-yl) izoindolin -1,3-dione (13). O-mesilylcinchonine **6** (1 g,0,00 26 mmol), TFE(3 ml), t-butylamonium hydrogensulphate(0,22g, 0,00085 mmol) and potasium phtalimide (1,44 g, 0,0078 mmol) was refluxed for 3 days. The reaction mixture was washed with sat. aq. $NaHCO_3$ and dried (Na_2SO_4). After removal of the solvent the crude product was purified by chromatography (ether:MeOH, 9:1) and resulted 0,2 g product (η=18%).H-NMR: (400 MHz, $CDCl_3$): δ 8,68(d, J=4,6, H-2'); 8,43(d, J=7,9, H-5'); 8,27(dd, J= 4,6. 9,6, H2", H5"); 8,13(d, J=8,2, H-8');7,78-7,72(m, H-7');7,69(m, H3", H4"); 7,47(d, J=4,5 H-3'); 5,97(ddd, J=6,8, 10,5, 17,2, H-10); 5,63-5,55(m,H-3); 5,21-5,11(m,H-11); 4,52(d, J=9,4, 14,3, H=7); 3,23-3,17(m, H-7); 2,37-2,32(m,H-8); 2,68(s, H2); 2,26-2,21(m, H-8, H-4); 2,11-2,06(m, H-6); 2,05-2,0(m, H4,H5); 1,92-1,82(m, H-9).$C_{27}H_{25}N_3O_2$(438,48): calc. C 73,58%, H 5,83%, N 9,63%; found C 73,71%, H 5,96%, N 9,48%.

3-Amino-2-(Quinolin–4-yl)-6-vinyl-1-aza-bicyclo-[3.2.2]nonane (14)
Compound **13** (0,13g, 0,0003 mol), hydrazine (0,2 ml, 0,004mol), ethanol (3ml) was heated at 60℃ for 5 hours. The reaction mixture was filtered, and then the solvent was removed. The residue was dissolved in DCM and then purified by column chromatography (eluent ether: ethanol 9:1) and resulted 0,052 g product ((η=52%).H-NMR: (400 MHz, $CDCl_3$): δ 8,78(d, J=4,6, H-2'); 8,38(d, J=8,1 H-5'); 8,05(d, J=7,8, H-8');7,58-7,51(m, H-7'); 7,44(d, J=6,1, G-6'); 7,34(d, J=4,6 H-3'); 5,89(ddd, J=6,8, 10,5, 17,2, H-10); 5,52-5,42(m, H-3); 5,33-5,23(m,H-11); 4,42(d, J=9,4, 14,3, H=7); 3,26-3,18(m, H-7); 2,86-2,77(m,H-8); 2,68(s, NH_2); 2,66-2,53(m, H-8, H-4); 2,37-2,28(m, H-6); 1,83-1,74(m, H4,H5); 1,72-1,61(m, H-9).$C_{19}H_{23}N_3$(293,39): calc. C 77,77%, H 7,90%, N 14,32%; found C 77.86%, H 8,04%, N14,20%.

REFERENCES

1. C.E. Song, **"**Cinchona Alkaloids in synthesis and catalysis" *,*Wiley-VCH,New-York **2009.**
2. W.M.Braje, R. Wartchow, H.M.R. Hoffmann, *Ang. Chem. Int. Ed*, **1999**, 2539.
3. C.Bolm, J.P.Hildebrand, K. Muniz, "Recent Advances in Ad and AA in Catalytic Asymmetric Synthesis", ed. I. Ojima, Wiley-VCH, New York, **2000.**
4. M. H. Franz, S, Roper, R. Wartchow, H.M.R. Hoffmann, *J.Org. Chem*, **2004**, *69*, 2983.
5. O. Schrake, H. M. Franz, R. Wartchow, H.M.R. Hoffmann, *Tetrahedron*, **2000**, *50*, 4453.
6. S. Roper, M.H. Franz, R. Wartchow, H.M.R. Hoffmann, *J. Or. Chem*.,**2003,** *68*,4944.
7. A.J.Mancuso, D. Swern, *Synthesis*, **1981,** 165.
8. H.M.R.Hoffmann, J. Frackenpohl, *Eur.J.Chem*,**2004,** 4293
9. O. Mitsunobu, M.Wada,T.Sano, *J.Am.Chem.Soc*,**1972,** *94*, 679