SYNTHETIC COMMUNICATIONS, 24(5), 701-707 (1994)

REDUCTION AND N-ALKYLATION OF α-METHYLENE -INDOLINES WITH SODIUM CYANOBOROHYDRIDE IN CARBOXYLIC ACIDS

Emília R. Balogh[1], *Béla Zsadon[1], Antal Csámpai[1] and Róbert Pál[2]

[1]Eötvös University Budapest, Institute of Chemistry
H-1518 Budapest 112, P.O.Box 32, Hungary
[2]Hungarian Oil and Gas Co. Development and Marketing Division
H-2443 Százhalombatta, P.O.B. 1, Hungary

ABSTRACT. The reaction of α-methylene-indolines with $NaCNBH_3$ in carboxylic acids at room temperature can yield either 2β,3β-dihydro-indolines or their N-alkyl derivatives as main products with high selectivity, depending mainly on the carboxylic acid and on the reaction time when using a large excess of $NaCNBH_3$.

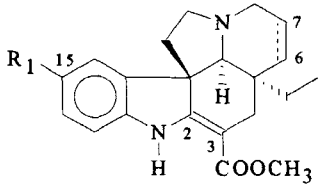
The reduction of indoles to indolines with $NaBH_4$ or $NaCNBH_3$ in carboxylic acids was published earlier[1,2]. Gribble et al.[1] have found that following the reduction N-alkylation also proceeds using $NaBH_4$, while $NaCNBH_3$ reduces selectively, without any formation of N-alkylated derivatives. Therefore, the use of $NaCNBH_3$ was suggested to selective reduction of indoles[1] and even for other aromatic N-heterocycles[3].

Later, Kumar et al.[2] have found the reduction of indoles with $NaCNBH_3$ in acetic acid to be only selective at room temperature, while at higher temperature (50 °C) reduced N-ethylated derivatives could also be produced.

* Author to whom correspondence should be addressed.

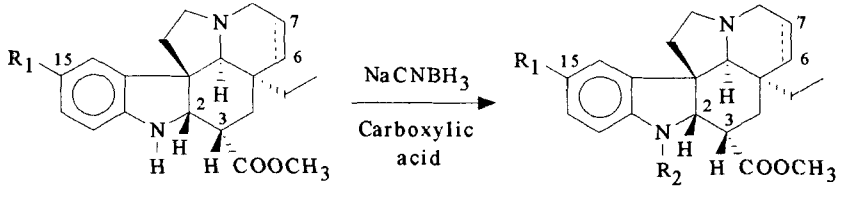
Other authors[4,5,6] published the selective reduction of alkaloids having α-methylene-indoline structure, e.g. tabersonine (**1a**) and its derivatives, with $NaCNBH_3$ in acetic acid without referring to the formation of any N-alkylated products or by-products.

We have systematically studied the reactions of the α-methylene-indoline alkaloids tabersonine (**1a**), vincadifformine (**1b**) and their 15-Br- and 15-NO_2- -derivatives (**2 a,b** and **3 a,b** resp.) with $NaCNBH_3$ in the carboxylic acids HCOOH, CH_3COOH and C_2H_5COOH. The reactions were carried out at room temperature (20 °C) using a molar ratio of $NaCNBH_3$ to the alkaloid 5:1.



	a	b
1 :R_1=H	Δ6,7	6,7-satd.
2 :R_1=Br	Δ6,7	6,7-satd.
3 :R_1=NO_2	Δ6,7	6,7-satd.

Carboxylic acid | $NaCNBH_3$



	a	b
4 :R_1=H	Δ6,7	6,7-satd.
5 :R_1=Br	Δ6,7	6,7-satd.
6 :R_1=NO_2	Δ6,7	6,7-satd.

R_2=alkyl
(CH_3, C_2H_5 or C_3H_7)

It could unambiguously be established that the transformation of each of our α-methylene-indolines under the given conditions involves the primary

formation of the 2β,3β-dihydro derivatives[7] (1 → 4, 2 → 5, 3 → 6), followed by their N-alkylation of different rates to give the final N-alkylated product corresponding to the carboxylic acid employed. These N-alkylated products could also be produced in separate steps by the reaction of isolated indolines with $NaCNBH_3$ in carboxylic acids.

N-acylation of the indolines, as a competitive reaction, could also be detected. However, in accord with the finding of Gribble et al.[1], under the applied conditions the N-acyl derivatives were not transformed into N-alkyl products.

Figure 1. demonstrates the course of these reactions in time by the example of the reaction of vincadifformine (**1b**) with $NaCNBH_3$ in acetic acid solution.

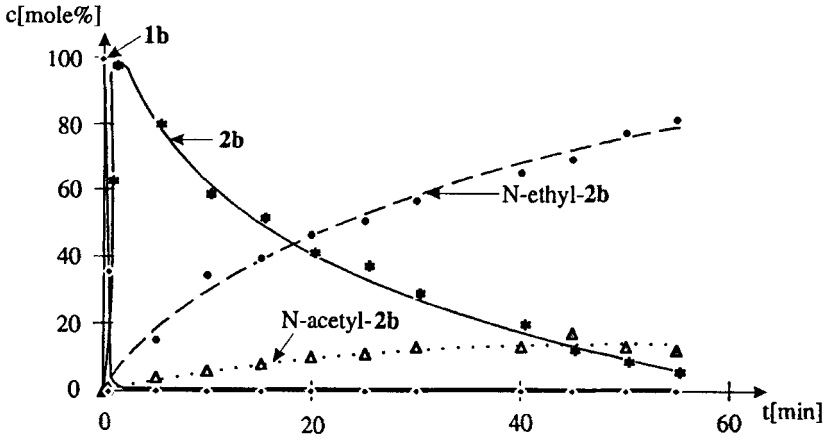


Figure 1. The time-function of the reaction of **1b** with $NaCNBH_3$ in acetic acid at 20 °C, detected by HPLC. The molar ratio of $NaCNBH_3$ to **1b** was 5:1.

The experimental results can be well utilized for preparative purposes. Namely, the reaction of α-methylene-indolines with $NaCNBH_3$ in carboxylic acids even at room temperature can yield either reduced indolines or their N-alkyl

derivatives as main products, depending above all on the carboxylic acid and on the reaction time applied.

Using a large excess of $NaCNBH_3$ especially in formic acid or acetic acid, α-methylene-indolines without any substituent on the aromatic ring or with 15-bromo-substitution can rather quickly be reduced (in several minutes) and their subsequent alkylation can practically be completed within a few hours. In this manner N-alkylated derivatives can easily be obtained with excellent stereo- and regio-selectivity in good yield.

On the other hand, the rate of N-alkylation is considerably decreased when applying a larger-sized carboxylic acid, such as propionic acid. (Under our experimental conditions using propionic acid, the conversion of indolines into N-propyl derivatives did not become complete even in a week.) Therefore, non--alkylated indolines can be prepared with high stereo- and regio-selectivity and good yield by a short-time treatment of α-methylene-indolines with $NaCNBH_3$ at room temperature in propionic acid.

Under the influence of highly electron-attracting substituent on the aromatic ring (e.g. NO_2 on the 15-position), the reduction and especially the N-alkylation proceed very slowly.

Our investigations resulted also in the syntheseis of several new 2β,3β--dihydro-indolenin alkaloid derivatives, the main characteristics of which are summarized in the Table.

EXPERIMENTAL

The course of the reactions in time were detected by HPLC. The chromatographic system consisted of a Varian 5000 pump, a Varian UV 100 detector and a Varian Vista 400 integrator. The UV detector was operated at 210

Table. Main characteristics of new N-alkylated 2β,3β-dihydro-indolenin alkaloid derivatives obtained by $NaCNBH_3$-reduction in acetic acid and *propionic acid, resp.

Product		Yield [%]	Most characteristic physical data[a]
N-ethyl-2β,3β-dihydro--tabersonine	N-ethyl-**4a**	80	m.p.=102.5-103.5 °C ; λ_{max}[nm]= 210; 258; 314 in MeOH ^{1}H-NMR: CH_3(N-Et) 1.02t (7.0Hz); OCH_3[b] 3.70s; H-2 3.95s; H-3[b] 3.80m
N-ethyl-2β,3β-dihydro--vincadifformine	N-ethyl-**4b**	81	m.p.=125-125.5 °C ; λ_{max}[nm]= 210; 258; 313 in MeOH ^{1}H-NMR: CH_3(N-Et) 1.02t (J=6.9Hz); OCH_3 3.72s; H-2 3.88d (2.0 Hz); H-3 4.10ddd (11.9, 6.5, 2.0 Hz)
15-bromo-N-ethyl-2β,3β--dihydro-tabersonine	N-ethyl-**5a**	94	m.p.=75-75.5 °C ; λ_{max}[nm]= 211; 267; 326 in MeOH ^{1}H-NMR: CH_3(N-Et) 1.00t (7.0 Hz); OCH_3[b] 3.70s; H-2 3.93s; H-3[b] 3.78m
15-bromo-N-ethyl-2β,3β--dihydro-vincadifformine	N-ethyl-**5b**	93	m.p.=157-157.5 °C ; λ_{max}[nm]= 211; 267; 326 in MeOH ^{1}H-NMR: CH_3(N-Et) 0.51t (6.3 Hz); OCH_3 3.73s; H-2 3.89d (1.8 Hz); H-3 4.09ddd (10.5, 5.5, 1.8 Hz)
*N-propyl-2β,3β-dihydro--vincadifformine	N-propyl-**4b**	51	colourless oil ; λ_{max}[nm]= 209; 258; 313 in MeOH ^{1}H-NMR: CH_3(N-Pr) 0.85t (6.9 Hz); OCH_3 3.71s; H-2 3.87d (1.9 Hz); H-3 4.12ddd (11.6, 6.7, 1.9 Hz)

[a]The NMR assignments are based on Ref. 7 [b]Partly overlapping signals

nm and 0.05 a.u.f.s.. A 150 mm x 4.6 mm i.d. SUPELCO C-18 5μm column was used at 30 °C. The mobile phase was 35% aqueous $(NH_4)_2CO_3$ (0.01 M) in CH_3CN. The flowrate was 2 ml/min.

The NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room tempetrature on a Bruker AC-80 PFT-spectrometer at 80 (^1H) with the deuterium signal of the solvent as the lock and TMS as internal standard.

General procedure

To a stirred solution of the substrate (1.2 mmole) in carboxylic acid (20 ml) $NaCNBH_3$ (6 mmole) was added in portions at room temperature. After the desired time the reaction mixture was poured onto ice then made alkaline and extracted with benzene. The organic layer was dried (Na_2SO_4), concentrated and the product was isolated by crystallization or chromatography.

Example 1. Reduction of vincadifformine (**1b**) *in propionic acid: 2β,3β-dihydro--vincadifformine* (**4b**)

To a stirred solution of vincadifformine (0.41 g, 1.2 mmole) in propionic acid (20 ml) $NaCNBH_3$ (0.38 g, 6 mmole) was added in portions at room temperature. After 10 minutes the reaction mixture was poured onto ice then made alkaline and extracted with benzene. The organic layer was dried (Na_2SO_4) and concentrated. The evaporation residue of the extract (0.4 g, 98%) was crystallized from ethanol: m.p.=70-71 °C; $[\alpha]_D^{20}$=+59 ° (c=0.2 in MeOH); λ_{max}[nm]=209, 249, 306. ^1H-NMR: NH(1) 4.32s; OCH_3 3.71s; H-2 3.94s/d (J<1 Hz); H-3 3.90m

Example 2. Reduction and alkylation of vincadifformine (**1b**): *N-ethyl-2β,3β--dihydro-vincadifformine* (N-ethyl-**4b**).

Vincadifformine (0.41 g, 1.2 mmole) was dissolved in acetic acid (20 ml). $NaCNBH_3$ (0.38 g, 6 mmole) was added to the solution and was stirred for 2 h at

room temperature. After the procedure described in the *Example 1.*, N-ethyl-**4b** (0.36 g, 81%) was crystallized from EtOH: m.p.=125-125.5 °C; $[\alpha]_D^{20}$=+11.2 ° (c=2 in MeOH); λ_{max}[nm]=210, 258, 313; ^{1}H-NMR: CH_3(N-Et) 1.02t(J=6.9Hz); OCH_3 3.72s; H-2 3.88d (2.0 Hz); H-3 4.10ddd (11.9, 6.5, 2.0 Hz).

REFERENCES AND NOTE

1. Gribble, G.W, Lord, P.D., Skotnicki, J., Dietz, S.E., Eaton, J.T., Johnson, J.L., J. Am. Chem. Soc., 1974, **96**, 7812.
2. Kumar, Y., Florwall, L., Synth. Commun., 1983, **13**(6), 489.
3. Gribble, G.W, Heald, P.W., Synthesis, 1975, 650.
4. Caron-Sigaut, C., Le Men-Olivier, L., Hugel, G., Lévy, J., Le Men, J., Tetrahedron, 1979,**35**, 957.
5. Kunesh, N., Miet, C., Poisson, J., Bull. Soc. Chim., 1982, 285.
6. Danieli, B., Lesma, G., Palmisano, G., Riva, R., J. Chem. Soc. Perkin Trans. I., 1987, 155.
7. The stereochemical reinvestigation of 2,3-dihydro-indolines by high-resolution NMR will be published shortly.

(Received in The Netherlands 10 August 1993)