SYNTHESIS WITH HYDROXYLACTAMES III[9] A FACILE ENTRY TO THE 1-OXO-ß-CARBOLINE SKELETON. SYNTHESIS OF STRYCHNOCARPINE

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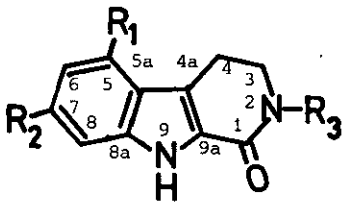
Abstract—Strychnocarpine 1c is synthesized via hydrogenation of 1-methyl-3-hydroxypyridone(2) with Ru/C. Fischer indole cyclization of phenylhydrazone 11 yields 1c.

Tricyclic indole alkaloids with the ß-carboline skeleton, the so-called "simple ß-carboline alkaloids" present a variety of modifications of the ring system mainly by the hydrogenation state of the pyridyl ring and are a well known class of pharmacodynamic active compounds[1].
In contrast the 1-oxo derivatives 1 are not so widespread in the pyrido[3,4-b]indole family.



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1a: R_1 = H R_2 = OCH_3 R_3 = H (from Banisteriopsis caapi)

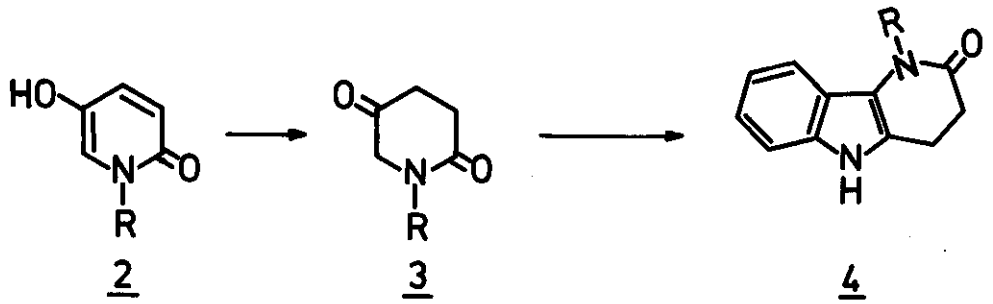
1b: R_1 = OCH_3 R_2 = H R_3 = H (from Alstonia venenata)

1c: R_1 = R_2 = H R_3 = CH_3 (Strychnocarpine)

1d: R_1 = R_2 = H R_3 =  (Rhetsinine)

Rhetsinine 1d was first isolated by Asahina and Ohta in 1926[2] later by other groups[2a,2b]. The correct structure was elucidated 1960[3]. Compound 1a was isolated in 1976[4] and the regioisomeric 1b in 1982[5]. Strychnocarpine 1c was isolated by W. Rolfsen et al.[6] and later by R. Verpoorte et al.[7] from strychnos species.

Its pharmacological properties as a weak muscle relaxant and 5-hydroxytryptamine receptor stimulator prompted us to look for a convenient entry into the 1-oxo-ß-carboline series and derivatives of strychnocarpine 1c, the latter of which was synthesized by Rolfsen in mg quantities via oxidation of harmalanmethosulfate[6]. In previous papers[8,9], we reported the catalytic hydrogenation of 5-hydroxy-2-pyridone 2 with Pd/C to piperidine-2,5-dione 3. Reaction of 3 with phenylhydrazines and Fischer indole synthesis yield the pyrido[3,2-b]indoles 4[10].



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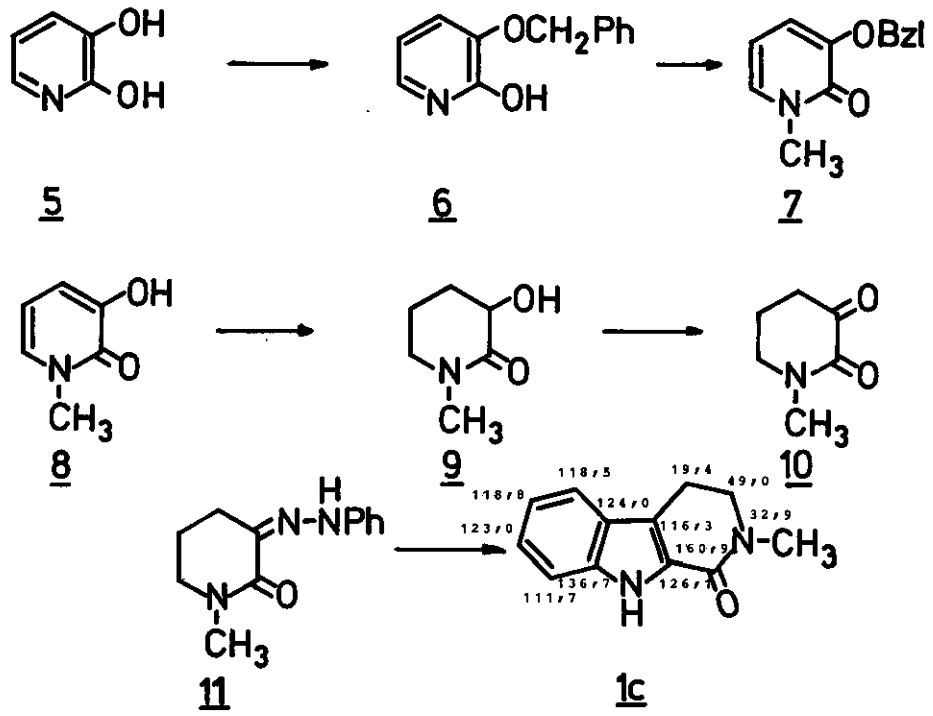
In this paper, we would like to report on a convenient method for the preparation of ketolactam 10 via 2,3-dihydroxypyridine 5 and its transformation to 1c.



5 6 7

8 9 10

11 1c

In contrast to 5-hydroxy-2-pyridone 2 (R=H) and its derivatives (R=CH_3,CH_2Ph), the regioisomeric 4- and 3-hydroxy-2-pyridones cannot be hydrogenated over Pd/C[11]. Möhrle and Weber[12] found that hydrogenation of 3-hydroxy-1-methyl-2-pyridone 8 under acidic conditions to 3-hydroxy-1-methyl-2-piperidone 9 was accompanied with loss of the hydroxy group.

Hydrogenation under neutral conditions should circumvent this problem. We tried the catalytic hydrogenation of 2,3-dihydroxypyridine in methanol with 5% Ru/C (Degussa)[13]. Complete reduction after 15h was accomplished. No trace of valerolactam could be detected. For the preparation of 8 we tried the N-methylation of 5 with methyl iodide according to the procedure of Möhrle and Weber[12].After several unsuccessfull attempts 8 could be isolated only in mg quantities. Therefore 5 was treated with benzyl bromide in KOH/MeOH. The resulting 3-benzyloxy-2-hydroxypyridine 6 could be N-methylated quantitatively with methyl iodide in DMSO/KOH[14]. Debenzylation by hydrogenation over Pd/C in methanol furnished 8 in quantitative yield. Hydrogenation over Ru/C gave in 95% yield after distillation 9[15]. Oxidation of 9 with Jones reagent led to ketolactam 10, which upon tretment with phenylhydrazine afforded the crystalline phenylhydrazone 11[16].

Fischer indole cyclization in formic acid provided strychnocarpine 1c. The ^{13}C chemical shift assignment of 1c was given by Rolfsen et al.[6].Since the chemical shift of the C-9a carbon atom was claimed to be 137.4 ppm, it should be revised. We found 126.1 ppm in accordance with the data in lit.[5,17].

With this procedure in hand various derivatives of strychnocarpine can be prepared for pharmacological screening and will be published in due course.

Table 1:

Compound	Molecular formula	C	H	N	^{1}H-NMR - δ = (ppm)
		Calcd.			
		Found			
6	$C_{12}H_{11}NO_2$	71.63	5.51	6.96	$CDCl_3$; δ = 5.23(s,2H), 6.20(t,J=7Hz,1H), 6.87 (dd,J=7/2Hz,1H), 7.15 (dd,J=7/2Hz,1H), 7.47 (s,5H), 13.5(s,1H)
		71.05	5.66	6.73	
7	$C_{13}H_{13}NO_2$	72.54	6.09	6.50	$CDCl_3$; δ = 3.63 (s,3H), 5.23 (s,2H), 6.08 (t,J=7Hz,1H), 6.77 (dd,J=7/2Hz,1H), 7.02 (dd,J=7/2Hz, 1H), 7.5 (s,5H).
		72.54	6.03	6.50	
8	$C_6H_7NO_2$	57.60	5.64	11.19	d_6-DMSO; δ = 3.60 (s,3H), 6.20 (t,J=7Hz,1H), 6.85 (dd,J=7/2Hz,1H), 7.25 (dd,J=7/2Hz,1H), 9.10 (s,1H).
		57.54	5.66	11.21	
9	$C_6H_{11}NO_2$	55.80	8.58	10.84	d_6-DMSO; δ = 1.5-2.0 (m,4H), 2.83 (s,3H), 3.1-3.3 (m,2H), 3.8 (m,1H), 5.03 (d,J=4Hz,1H).
		55.36	8.42	10.74	
11	$C_{12}H_{15}N_3O$	66.34	6.96	19.34	d_6-DMSO; δ = 1.9-2.1 (m,2H), 2.5-2.7 (m,2H), 3.0 (s,3H), 3.4 (m,2H), 7.4 (s,5H), 9.6 (s,1H).
		66.57	6.98	19.10	
1c	$C_{12}H_{12}H_2O$	71.98	6.04	13.99	$CDCl_3$; δ = 3.10 (t,J=7Hz,2H), 3.27 (s,3H), 3.77 (t,J=7Hz,2H), 7.1-7.8 (m,4H), 10.50 (s,1H).
		71.82	5.97	13.88	

EXPERIMENTAL

Infrared spectra were run on a Beckman Acculab 6. Nmr spectra were recorded on a Varian EM 360 A or a Brucker WP 80 with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. 2,3-Dihydroxypyridine was purchased from EGA and ALDRICH company. The mps are uncorrected. Rf values are quoted for Merck silicagel 60 GF_{254} TLC plates of thickness 0.25 mm. Detection: Jodine vapor. All experiments were run under nitrogen atmosphere.

3-Benzyloxy-2-hydroxypyridine (6)

To a stirred solution of KOH (2.24 g, 40 mmol) in 50 ml of MeOH, 2,3-Dihydroxypyridine (4.44 g, 40 mmol) was added in 5 portions. To the clear deep red solution benzyl bromide (5.22 ml, 44 mmol) was added. Stirring is continued first at ambient temperature for 30 min, then 2 h at 40°C. MeOH and the excess of benzyl bromide was then distilled off under reduced pressure. The residue was treated with water and extracted 3 times with CH_2Cl_2. The combined extracts were dried and the solvent was evaporated to give 6.87 g of unpurified material.Recrystallisation from EtOH yield 4.3 g

(53.4%) of pure material, mp 139-142°C, Rf=0.75 ($CHCl_3$/MeOH 9+1).

3-Benzyloxy-1-methyl-2-pyridinone (7)

To a solution of 6 (41.6 mmol, 8.36 g) in DMSO powdered KOH (62.4 mmol, 3.5 g) (1.5 fold excess) was added with stirring. After 10 min MeI (62.4 mmol, 8.85 g) was added dropwise with cooling. Stirring was continued for 2 h. The solvent was removed by evaporation. 300 ml H_2O was added and extracted 3 times with CH_2Cl_2. The combined extracts were washed with H_2O, dried and the solvent was evaporated. The brown oil (92.5% crude material) was distilled bp. 157-160°C ($1.1\ 10^{-2}$ mbar). After distillation the clear viscous oil solidified upon treatment with ether to afford 7.4 g (82.8%) colourless material, mp 68-69°C, Rf=0.35 (ethyl acetat).

3-Hydroxy-1-methyl-2-pyridinone (8)

A solution of 7 (30 mmol, 6.45 g) in MeOH was hydrogenated at ambient temperature over Pd/C (200 mg). After 1 h the catalyst was filtered off and the solution concentrated in vacuo to dryness. Yield quantitative (3.7g). For an analytical sample the product was recrystallized from acetonitrile or ligroin, mp 124-126°C, Rf=0.75 ($CHCl_3$/MeOH 9+1).

3-Hydroxy-1-methyl-2-piperidinone (9)

The residue obtained by the hydrogenation of 7 was dissolved in MeOH and hydrogenated over 3 g Ru/C[7] (50°C, 3 bar). After 12-15 h when no starting material was present (chromatographic control, ($CHCl_3$/MeOH, 9+1)) the catalyst was filtered off, washed with MeOH, and the solvent was evaporated. The colourless oil was distilled. bp 127-130°C (11 mm) (lit.[15,16] mp 79-82°C). Yield 28.5 mmol (3.68 g; 95.1 %).

3-Keto-1-methyl-2-piperidinone (10)

To an icecooled solution of 9 (30 mmol, 3.87 g) in 150 ml of acetone Jones reagent was added dropwise under rapid stirring until the suspension became slightly yellow (about 7.8 ml). After 10 min, the supernatant acetone is decolorized with isopropanol. The salt was filtered off and thoroughly rinsed several times with acetone. The combined solution was concentrated under reduced pressure. The oily

residue was dissolved in CH_2Cl_2, dried with Na_2SO_4 and concentrated in vacuo to give 1.9 g (49.8%) of 10[16].

2,3,4-Tetrahydro-2-methyl-1-oxo-1H-pyrido[3,4-b]indole, strychnocarpine (1c)[17]

Compound 10 (1.9 g) was treated with 1.6 g of phenylhydrazine. After a slight exothermic reaction the viscous oil crystallized. The yellow powder was washed with ether and a sample was recrystallized from isopropanol, mp 186-187°C (lit.[9] 186-188°C), Rf = 0.69 ($CHCl_3$/MeOH 9+1). The crude material was treated with formic acid (bath temp, 80°C). After 30 min the mixture was poured into water and extracted 3 times with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated. The residue was recrystallized from ethyl acetate. Slightly yellow crystals, mp 226°C (lit.[6] 198-200°C), Rf = 0.58 (ethyl acetate), yield 1.78 g (55.1%). ^{13}C-NMR(d_6-DMSO): δ(ppm) = C1 160.9 (s), N-CH_3 32.9 (q), C3 49.0 (t), C4 19.4 (t), C4a 116.3 (s), C5a 124.0 (s), C5 118.5 (d), C6 118.8 (d), C7 123.0 (d), C8 111.7 (d), C8a 136.7 (s), C9a 126.1 (s). IR(KBr): 3205 (NH), 2930, 2840, (CH), 1630 (C=O), 1610 (C=C), 1550, 1510, 1390, 1320, 1240, 1070, 765, 735 cm^{-1}. UV(MeOH) λ_{max} = nm(log ε): 227 (4.25), 242(4.07) 305 (4.14).

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