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Nitrogen Bridgehead Compounds 87[1]. Synthesis of 3-Azarutecarpine (14-Azanauclefine) and Its 7-Methyl Derivative

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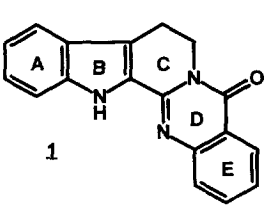
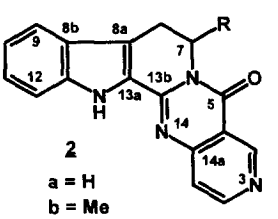
Abstract : 3-Azarutecarpine (14-azanauclefine) derivatives **2** were prepared by Fischer indolization of 6-phenylhydrazono-6,7,8,9-tetrahydro-11*H*-dipyrido[1,2-*a*;4,3-*d*]pyrimidine-11-ones **8**. Compounds **8** were obtained from 6,7,8,9-tetrahydro-11*H*-dipyrido-[1,2-*a*;4,3-*d*]pyrimidinones **7** with phenyldiazonium chloride. New compounds are characterized by UV, IR, ^{1}H and ^{13}C NMR spectroscopy.

INTRODUCTION

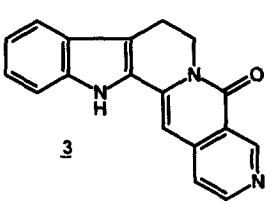
Earlier we developed a facile synthesis of rutecarpine alkaloid **1** starting from 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one alkaloid *via* Fischer indolization of 6-phenylhydrazono-11*H*-pyrido-[2,1-*b*]quinazolin-11-one[2]. Rutecarpine occurs in the genera *Evodia*, *Hortia*, and *Zanthoxylum*[3], and was a constituent part of traditional Chinese folk medicines, Whu-Chu-Yu[4] and Shih Hu[5]. Because rutecarpine and its derivatives command interest as hypertensive, diuretic, and uterotonic agents in the modern literature[6], we extended this new approach to synthesis of substituted derivatives of rutecarpine in rings A, C, and E [7], their 1,2,3,4-tetrahydro derivatives[8], its C-ring homologs[9], C-ring opened analogs[10], and E-ring debenzo derivatives[1].



1



2
a = H
b = Me

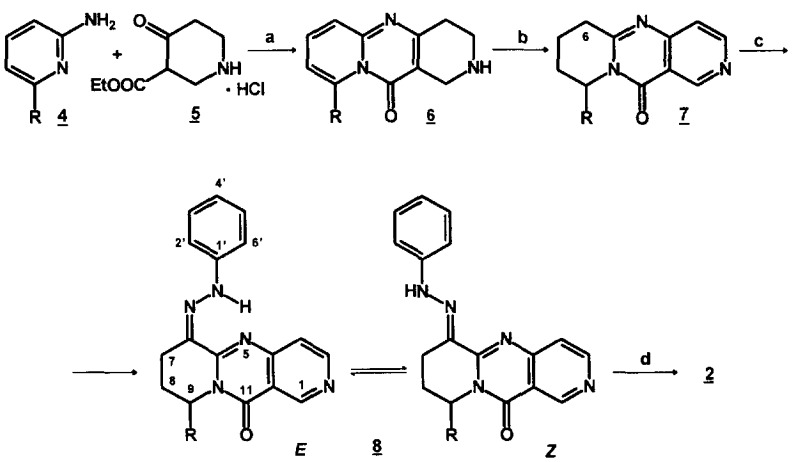


3

In this paper we describe the preparation of 3-aza derivative **2a** of rutecarpine **1**, and its 7-methyl derivative **2b** by the application of Fischer indole synthesis[11]. Compound **2a**, which is the first representative of a new pentacyclic ring system, can be also considered as the 14-aza derivative of nauclefine alkaloid **3**, which was isolated from the genera *Nauclea*[12].

RESULTS AND DISCUSSION

1,2,3,4-Tetrahydro-11*H*-dipyrido[1,2-*a*;4,3-*d*]pyrimidin-11-ones **6** were obtained by cyclocondensation of 3-ethoxycarbonyl-4-piperidone hydrochloride **5** and 2-aminopyridines **4** in PPA at 120 °C according to the known process[13, 14]. Hydrogen transfer[15] of 1,2,3,4-tetrahydro derivatives **6** in boiling xylene in the presence of 10% Pd / C catalysts gave 6,7,8,9-tetrahydro-11*H*-dipyrido[1,2-*a*;4,3-*d*]pyrimidin-11-ones **7**. Reaction of the active methylene group of **7** at position 6 with phenyldiazonium chloride[16] resulted in 6-phenylhydrazono derivatives **8**. This type of reaction[17] was earlier applied to similarly situated active methylene groups[8,18]. Fischer indolization of phenylhydrazono compounds **8** was carried out in polyphosphoric acid (PPA) at 180 °C to give pentacyclic 3-azarutecarpine derivatives **2** in good yields (see Scheme 1 and experimental).



Scheme 1: a: PPA 120 °C, 6h. b. Δ/xylene/Pd-C, 7h, c: $PhN_2^+Cl^-$, AcONa, 50% AcOH, 0-5 °C. d: PPA, 180 °C, 30 min.

Some characteristic UV, IR, ^1H and ^{13}C NMR data are tabulated in Tables 1 - 3. The hypsochromic shift of the absorption band at the highest wavelength of 6,7,8,9-tetrahydro derivatives **7** comparing with that of 1,2,3,4-tetrahydro derivatives **6**, is reflecting the higher aromatic character of the former.

The formation of 6,7,8,9-tetrahydro derivatives **7** from 1,2,3,4-tetrahydro derivatives **6** is justified by the similar chemical shifts of 6,7,8,9-methylene protons in compounds **7**, as was found at the 2-deaza derivative

6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones[19], and by the appearance of the doublet ($J_{9,Me}$ ~ 6.5) of methyl group in compound **7b**.

Table 1. Some UV and IR Data for Compounds **2** and **6-8** in EtOH and KBr, respectively.

Comp.	λ_{max} (ε) nm							ν_{CO} cm^{-1}
2a	365 (31600)	353 (32100)	290 (7000)	280inf (6900)	244 (17800)	233 (20500)	214 (29700)	1668
2b	364 (23800)	355 (24000)	290 (6000)	283inf (5900)	244 (13700)	234 (15400)	215 (23000)	1670
6a		342 (10100)	331 (10100)	253inf (9300)	245 (10900)	216inf (15700)		1670
6b		356 (8800)	327inf (6950)	258inf (9750)	252 (10600)	221inf (13500)		1676
7a		282 (8750)	224 (18500)					1675
7b		283 (9050)	225 (17600)					1671
8a	403 (21800)	300inf (7000)	293 (7350)	253 (16350)	229 (17500)			1688
8b	400 (23700)	301inf (7400)	293inf (7600)	252 (16500)	229 (17600)			1670

inf = inflexion

Both the chemical shift and the values of coupling constants indicate the quasiequatorial orientation of the proton in the position 9 at compounds **6b**, **7b**, **8b**, and in position 7 at compound **2b**, so the methyl group occupies the quasiaxial position to avoid 1,3-allylic strain, which would be presence in the alternative conformation[20]. The 6-phenylhydrazono derivatives **8** exhibit a solvent dependent *E* - *Z* geometric isomerism, indicating a low activation energy of the process around the exo cyclic C(6)=N double bond[21,22]. In $CDCl_3$ the sterically more crowded *Z* form is favourable, because the presence of an internal hydrogen bond between the amino group and ring nitrogen atom, while in DMSO-d_6 ,which solvent forms a more stronger hydrogen bridge with the amino group than $CDCl_3$, the sterically more favourable *E* form is predominant. In $CDCl_3$ the E - Z ratio is 96 : 4 and 94 : 6, and in DMSO- d_6 32 : 68 and 24 :76 for compounds **8a** and **8b**, respectively.

The assignment of ^{13}C chemical shifts of compounds **2** and **8** was determined on the basis of analog debenzo rutecarpine derivatives[1], and rutecarpine and nauclefine[23], and 9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyri-do[1,2-*a*]pyrimidin-4-ones[22], and furthermore they were confirmed by determination of the signal multiplicities from DEPT - 135 spectra.

EXPERIMENTAL

Melting points were determined on a Beotius hot plate and are uncorrected. Yields were not optimized. The UV spectra were recorded on a Perkin Elmer Lambda 14 spectrophotometer in ethanol. The IR spectra were recorded for KBr pellets with a Bruker IFS-28 spectophotometer. The ^1H and ^{13}C nmr spectra were

Table 2: ^{1}H Chemical Shifts (ppm) and Coupling Constants (Hz) of Compounds **2** and **6 - 8** in DMSO-d_6.

	2a	**2b**		**6a**	**6b**	**7a**	**7b**	**8a-*Z*[a]**	**8a-*E*[a]**	**8a-*Z***	**8a-*E***	**8b-*Z*[a]**	**8b-*E*[a]**	**8b-*Z***	**8b-*E***
1-H	7.66	7.55	1-H	3.68	3.82	9.23	9.44	9.49	9.49	9.27	9.23	9.50	9.49	9.27	9.24
2-H	8.78	8.80	3-H	2.97	3.12	8.74	8.74	8.83	8.80	8.85	8.74	8.84	8.81	8.84	8.74
4-H	9.26	9.30	4-H	2.63	2.68	7.44	7.36	7.45	7.63	7.93	7.57	7.47	7.65	7.91	7.56
7-H	4.44	5.54	6-H	7.50	7.23	2.93	3.15-2.90								
8-H	3.20	3.37; 3.21	7-H	7.80	7.30	1.87	2.10-1.95	2.90	2.76	2.79	2.73	3.15-2.85	2.85-2.75	3.05-2.70	2.85-2.70
9-H	7.55-7.05	7.69	8-H	7.21	6.53	1.87	2.10-1.95	2.16	2.21	2.07	2.07	2.10-2.05	2.30-2.05	2.20-2.05	2.20-2.05
10-H	7.55-7.05	7.12	9-H	8.80		3.93	5.06	4.11	4.23	3.99	4.10	5.20	5.43	4.97	5.18
11-H	7.55-7.05	7.31	NH					14.59	8.14	14.44	10.11	14.77		14.61	10.14
12-H	7.55-7.05	7.50	2'-H					7.28		7.45-7.25	7.45-7.25	7.40-7.28	7.40-7.28	7.45-7.25	7.45-7.25
13-H	11.99	12.02	3'-H					7.35		7.45-7.25	7.45-7.25	7.40-7.28	7.40-7.28	7.45-7.25	7.45-7.25
			4'-H					7.02		6.97	6.93	7.04	7.04	6.98	6.93
			5'-H					7.35		7.45-7.25	7.45-7.25	7.40-7.28	7.40-7.28	7.45-7.25	7.45-7.25
			6'-H					7.28		7.45-7.25	7.45-7.25	7.40-7.28	7.40-7.28	7.45-7.25	7.45-7.25
Me		1.29	Me		2.99		1.37					1.43	1.38	1.33	1.26
$J_{1,2}$	6.0	3.1	$J_{3,4}$	5.7	5.9	5.7	5.6	5.6	5.8	5.7	5.7	5.6	5.7	5.2	5.6
$J_{7,8}$	6.8	6.7; 1.0	$J_{6,7}$	8.9	9.0	6.5									
			$J_{6,8}$	1.5	0.9										
			$J_{7,8}$	6.8	6.2			6.2	6.8	6.0	6.7				
			$J_{7,9}$	1.2											
			$J_{8,9}$	7.2		6.0		5.9		5.7					
$J_{7,Me}$		6.7	$J_{9,Me}$				6.5					6.4	6.4	6.4	6.4

[a] in $CDCl_3$

acetic acid in **8b**:1.91 DMSO; 2.11 $CDCl_3$

measured on a Bruker DRX-400 spectrometer at 400.13MHz and 100.64MHz, respectively. Chemical shifts are given on δ scale, and TMS was used as internal standard.

Preparation of 1,2,3,4-Tetrahydro-11H-dipyrido[1,2-a;4,3-d]pyrimidin-11-ones **6a,b.**

3-Ethoxycarbonyl-4-piperidone hydrochloride **5** (120 mmoles) and the appropriate 2-aminopyridine **4** (120 mmoles) were stirred in PPA (130 g) at 120 °C for 6 h. To the reaction mixture water (130 ml) was added at 70 °C, then the pH of the cooled mixture was adjusted to 9 by the addition of 10% sodium hydroxide solution at 0°C. The reaction mixture was extracted with chloroform (5 x 200 ml). The combined and dried (over Na_2SO_4) organic solvent was evaporated in vacuo to dryness, and the residue was crystallized from ethyl acetate.

6a : yield 77%, mp: 140 - 142 °C. Lit. mp: 127 - 129 °C[13].

6b : yield 78%, mp: 135 - 137 °C. Lit. mp: 134 - 135 °C[13] and 135 -136 °C[14].

Table 3: ^{13}C Chemial Shifts (ppm) of Compounds **2** and **8** in DMSO-d_6

	2a	**2b**		**8a**-*Z*	**8a**-*E*	**8b**-*Z*	**8b**-*E*
C-1	120.5[a]	120.6[b]	C-1	153.3	152.9	153.3	152.9
C-2	150.1	149.9[c]	C-3	149.6	150.0	149.7	150.0
C-4	153.4	152.9	C-4	120.1	120.6	120.0	120.6
C-4*a*	120.1	120.3[b]	C-4*a*	150.5[g]	152.6[h]	150.5[i]	152.5[j]
C-5	160.3	159.8	C-5*a*	151.2[g]	153.4[h]	150.7[i]	152.6[j]
C-7	41.0	47.4	C-6	124.8	133.6	123.6	132.6
C-8	19.0	25.2	C-7	30.6	24.4	25.5[d]	20.1
C-8*a*	116.6	118.0	C-8	20.6	19.6	25.8[d]	24.1
C-8*b*	126.8[e]	125.9[f]	C-9	42.9	40.5	47.1	45.4
C-9	120.2[a]	120.5[b]	C-11	160.1	160.3	159.5	159.9
C-10	119.8[a]	120.2[b]	C-11*a*	115.6	115.6	115.7	115.7
C-11	125.7	125.8[f]	C-1'	143.4	144.6	143.3	144.6
C-12	112.9	113.0	C-2'	114.0	114.3	114.2	114.3
C-12*a*	139.3	139.7	C-3'	129.5	129.2	129.5	129.2
C-13*a*	124.9[e]	125.7[f]	C-4'	122.1	121.4	122.3	121.5
C-13*b*	149.5	148.4	C-5'	129.5	129.2	129.5	129.2
C-14*a*	152.7	153.0[e]	C-6'	114.0	114.3	114.2	114.3
Me		18.8				17.8	17.0

[a, b, c, d, e, f g h, i, j] = interchangeable signals

acetic acid in **8b**:172.2, 21.2.

Preparation of 6,7,8,9-tetrahydro-11H-dipyrido[1,2-a;4,3-d]pyrimidin-11-ones **7a,b.**

A solution of 1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*;4,3-*d*]pyrimidin-11-one **6** (93 mmoles) was refluxed in xylene (130 ml) for 7 h in the presence of 10% Pd/C catalysts (9 g). After filtration of the catalysts

the reaction mixture was washed with chloroform (150 ml). The combined organic layer was evaporated in vacuo to dryness, and the residue was crystallized from ethyl acetate.

7a: yield 67%, mp: 152 - 155 °C. Elemental analysis for $C_{11}H_{11}N_3O$: Found: C 65.81%, H 5.47%, N 20.82%; calculated: C 65.66%, H 5.51%, N 20.88%.

7b: yield 41%, mp: 115 - 118 °C. Lit. mp: 117 - 119 °C[15].

Preparation of 6-phenylhydrazon-6,7,8,9-tetrahydro-11H-dipyrido[1,2-a;4,3-d]pyrimidin-11-ones **8a,b**

To a solution of phenyldiazonium chloride, prepared from aniline (10 mmoles) with sodium nitrite in 1:1 hydrochloric acid (5 ml) at 0 - 5 °C, sodium acetate (3.3 g), then a solution of 6,7,8,9-tetrahydro-11*H*-dipyrido[1,2-*a*;4,3-*d*]pyrimidin-11-one **7** in 50% acetic acid were added dropwise. The reaction mixture was stirred for 3 h at 0 -5 °C, and it was allowed to stand in a refrigerator overnight. The precipitated crystals were filtered off, washed with water and were boiled in ethanol.

8a: yield 93%, mp: 219 - 223 °C. Elemental analysis for $C_{17}H_{15}N_5O$: Found: C 67.06%, H 4.94%, N 22.86%; calculated: C 66.87%, H 4.95%, N 22.94%.

8b: yield 95%, mp: 175 - 177 °C. Elemental analysis for $C_{18}H_{17}N_5O$•AcOH: Found: C 63.31%, H 5.58%, N 18.46%; calculated: C 63.47%, H 5.45%, N 18.64%

Fischer Indolization of Compounds **8**.

To PPA (10 g, Fluka) at 180 °C 6-phenylhydrazon-6,7,8,9-tetrahydro-11*H*-dipyrido[1,2-*a*;4,3-*d*]-pyrimidin-11-one **8** (3.3 mmoles) was added and the reaction mixture was stirred for 30 min. Then water (100 ml) was added to it at ambient temperature, and the aqueous mixture was stirred for 1 h. The precipitated crystals were filtered off, treated with 10% sodium hydroxide solution, and water. The dried crystals were crystallized from dimethylformamide.

2a : yield 71%, mp: 302 - 304 °C. Elemental analysis for $C_{17}H_{12}N_4O$: Found: C 70.75%, H 4.28%, N 19.49%; calculated: C 70.82%, H 4.20%, N 19.43%.

2b : yield 40%, mp: > 305 °C. Elemental analysis for $C_{18}H_{14}N_4O$: Found: C 71.70%, H 4.58%, N 18.48%; calculated: C 71.51%, H 4.67%, N 18.53%.

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