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Fischer indolization of 6-arylhydrazono-6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-ones **1** afforded substituted 7,8-dihydro-5H,13H-indolo[2',3':3,4]pyrido[2,1-b]quinazolin-5-ones **3-12** in high yields.

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We recently reported [2] a facile total synthesis of rutecarpine alkaloid **3** ( $R = R^1 = R^2 = H$ ) [3] starting from 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one alkaloid **1** ( $R = H$ ) [4] via the 6-phenylhydrazone derivative **2** ( $R = R^1 = R^2 = H$ ). Fischer indolization of compound **2** ( $R = R^1 = R^2 = H$ ) in polyphosphoric acid afforded rutecarpine **3** ( $R = R^1 = R^2 = H$ ) in high yield [2]. Rutecarpine and its derivatives command interest as hypertensive [5,6], diuretic [7,8] and uterotonic [7,9,10] agents.

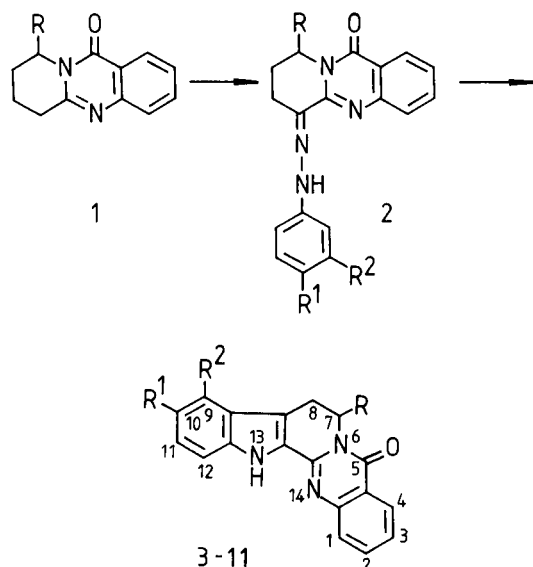
on the action of heat (Method A), and in the presence of Lewis acids, e.g. zinc chloride (Method B) or polyphosphoric acid (Method C).

When the hydrazones **2** were heated in Dowtherm A at 240°, pentacyclic indole derivatives were obtained only in low yield (16-20%) because of tar formation. Higher yields (~50%) could be achieved if the hydrazones **2** were heated in zinc chloride at 200° (see Table 1).

After the hydrazones **2** were heated in ethanol or acetic acid in the presence of hydrogen chloride, or in formic acid, pentacyclic indole derivatives could not be detected by means of thin-layer chromatography. Polyphosphoric acid proved to be more useful cyclizing agent than concentrated sulfuric acid or 85% phosphoric acid for the preparation of indolopyridoquinazolinones.

In polyphosphoric acid, higher yields of indolopyridoquinazolinones could be achieved by starting from the hydrochloride salt of the hydrazones **2**. If the phenyl group of the starting hydrazones **2** contained a *p*-nitro or *p*-trifluoromethyl substituent, the pentacyclic ring system was not formed at 180°, while decomposition of the hydrazones **2** took place at higher temperatures.

Scheme



In this paper we give an account of our further investigations on the applicability of Fischer indolization [11] in the preparation of rutecarpine derivatives.

#### Synthesis.

Fischer indolization of the arylhydrazonotetrahydropyridoquinazolinones **2** [12] was carried out in Dowtherm A

#### Spectroscopic Studies.

The uv spectra of indolopyridoquinazolinones **3-11** have a characteristic absorption band at 330-370 nm, with fine structure. The intensity and wavelength of this band proved to be not very sensitive to the nature of the substituents in positions 7 and 10 (see Table 2).

In the pmr spectra of compounds **3-11** the signal of the 7-methylene groups appears at 4.40-4.90 ppm, and that of the 8-methylene group at 3.10-3.60 ppm. The downfield shift of the H-7 signal for compound **4** suggests that the 7-methyl group occupies a quasi-axial position. The quasi-equatorial position is highly disfavoured because of 1-3 allyl-type strain [13,14] caused by the neighbouring carbonyl group.

Table 1  
 5*H*,13*H*-Indolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5-ones **3-11**

Product	R	R <sup>1</sup>	R <sup>2</sup>	Method	Reaction period (minutes)	Yield %	Mp, °C (solvent)	Formula Molecular Weight	Analysis %		
									C	H	N
<b>3</b>	H	H	H	A	20	20	255-256 [a] (DMF)	C <sub>18</sub> H <sub>13</sub> N <sub>3</sub> O 287.323	75.24	4.56	14.52
									75.19	4.55	14.16
<b>3</b>	H	H	H	B	30	58	258-260 [a] (DMF)		75.24	4.56	14.52
									75.21	4.56	14.58
<b>3</b>	H	H	H	C	20	94	260-261 [a] (DMF)		75.24	4.56	14.56
									75.28	4.54	14.51
<b>3</b>	H	H	H	C [b]	20	98	260-261 [a] (DMF)		75.24	4.56	14.56
									75.16	4.60	14.57
<b>4</b>	H	H	Me	A	20	16	225-227 (DMF)	C <sub>19</sub> H <sub>13</sub> N <sub>3</sub> O 301.350	75.72	5.01	13.94
									75.85	5.05	13.88
<b>4</b>	H	H	Me	C	30	48	226-228 (DMF-EtOAc)		75.72	5.01	13.94
									75.76	5.02	13.90
<b>4</b>	H	H	Me	C [b]	30	67	226-228 (DMF-EtOAc)		75.72	5.01	13.94
									75.68	4.95	13.96
<b>5</b>	Me	H	H	B	30	62	230 (DMF-EtOAc)	C <sub>19</sub> H <sub>15</sub> N <sub>3</sub> O 301.350	75.72	5.01	13.94
									75.43	4.99	14.05
<b>5</b>	Me	H	H	C	30	64	230 (DMF-EtOAc)		75.72	5.01	13.94
									75.71	5.02	13.99
<b>6</b>	F	H	H	C	20	79	302 (DMF-EtOAc)	C <sub>18</sub> H <sub>12</sub> N <sub>3</sub> OF 305.314	70.81	3.96	13.76
									70.85	4.01	13.72
<b>7</b>	Cl	H	H	C	20	81	312-314 (EtOAc)	C <sub>18</sub> H <sub>12</sub> N <sub>3</sub> OCl 321.769	67.19	3.76	13.05
									67.24	3.81	13.01
<b>8</b>	Br	H	H	C	20	67	284 (DMF)	C <sub>18</sub> H <sub>12</sub> N <sub>3</sub> OBr 366.225	59.03	3.30	11.47
									59.11	3.35	11.40
<b>9</b>	OPh	H	H	C	20	41	267-268 (EtOAc)	C <sub>24</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> 379.421	75.97	4.51	11.07
									76.09	4.55	11.02
<b>10</b>	CN	H	H	C	30	92	255 (DMF)	C <sub>19</sub> H <sub>12</sub> N <sub>4</sub> O 312.334	73.06	3.87	17.53
									73.09	3.88	17.84
<b>11</b>	-(CH=CH) <sub>2</sub> -	H	H	C	30	89	298 (DMF)	C <sub>22</sub> H <sub>15</sub> N <sub>3</sub> O 337.383	78.32	4.48	12.45
									78.51	4.60	12.21

[a] Lit [3] mp 258°. [b] Starting from the hydrochloride salt of **2**.

Table 2  
 UV Data on 5*H*,11*H*-Indolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5-ones **3-10** in Ethanol

Compound	R	R <sup>1</sup>	R <sup>2</sup>	λ max (log ε)					
<b>3</b>	H	H	H	364 (4.44)	345 (4.54)	332 (4.49)	290 (3.88)	278 (3.83)	
<b>4</b>	Me	H	H	362 (4.39)	344 (4.52)	331 (4.47)			
<b>5</b>	H	Me	H	364 (4.37)	346 (4.49)	332 (4.41)	291 (3.85)	278 (3.80)	266 (4.52)
<b>6</b>	H	H	F	362 (4.35)	345 (4.45)	330 (4.37)	292 (3.91)	277 (3.79)	
<b>7</b>	H	Cl	H	364 (4.40)	347 (4.51)	332 (4.43)	290 (3.92)	277 (3.84)	
<b>8</b>	H	Br	H	364 (4.43)	349 (4.54)	335 (4.49)	292 (3.87)	279 (3.80)	
<b>9</b>	H	O	H	362 (4.36)	350 (4.50)	334 (4.39)	293 (3.89)	281 (3.78)	
<b>10</b>	H	CN	H	364 (4.28)	347 (4.44)	334 (4.30)	293 (3.91)	282 (3.93)	

## EXPERIMENTAL

Melting points are uncorrected. The uv spectra were recorded on an UNICAM SP-800 spectrophotometer, and pmr spectra on a Bruker WP-80 Ft spectrometer with tetramethylsilane as internal standard.

### Method A. Indolization on the Action of Heat.

Hydrazonotetrahydropyrido[2,1-*b*]quinazolinone (**2**) (1 g) was added to Dowtherm A (20 ml) at 220°, and the reaction temperature was raised to 240°. After a 20 minute reaction period, the reaction mixture was cooled to ambient temperature. The precipitated crystals were filtered off and

Table 3

PMR Data on 5*H*,11*H*-Indolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5-ones **3-11**

Compound	R	R <sup>1</sup>	R <sup>2</sup>	Solvent	8-CH <sub>2</sub>	7-CH <sub>2</sub>	R or R <sup>1</sup>	Ar-H
<b>1</b>	H	H	H	Deuteriochloroform	3.21 t	4.58 t		7.3-7.8 m
<b>4</b>	Me	H	H	Deuteriochloroform	3.15 d	5.52 m	1.36 d	7.0-7.6 m
<b>5</b>	H	Me	H	Deuteriochloroform	3.18 t	4.56 t	2.46 s	7.0-7.8 m
<b>6</b>	H	F	H	DMSO-d <sub>6</sub>	3.15 t	4.43 t		6.9-8.0 m
<b>7</b>	H	Cl	H	DMSO-d <sub>6</sub>	3.28 t	4.53 t		7.1-8.1 m
<b>8</b>	H	Br	H	Deuteriochloroform	3.42 t	4.56 t		7.0-8.0 m
<b>9</b>	H	OPh	H	DMSO-d <sub>6</sub>	3.47 t	4.58 t		7.1-8.5 m
<b>10</b>	H	CN	H	TFA	3.50 t	4.81 t		7.3-8.2 m
<b>11</b>	H	(CH=CH)-		DMSO-d <sub>6</sub>	3.56 t	4.53 t		7.2-8.4 m

washed with ethanol. The product was dissolved in dimethylformamide and the resulting solution was clarified with active carbon. The filtrate was diluted with ethyl acetate or water. The precipitated indolopyridoquinazolinone was filtered off, dried and recrystallized.

#### Method B. Indolization with Zinc Chloride.

A mixture of hydrazone tetrahydropyrido[2,1-*b*]quinazolinone (**2**) (1 g) and anhydrous zinc chloride (5 g) was heated at 200° for 30 minutes. The cooled reaction mixture was treated with water (50 ml). The precipitated crystals were filtered off and dissolved in chloroform, the chloroform solution was clarified with active carbon. The dried (sodium sulfate) solution was evaporated. The residue was recrystallized to give the indolopyridoquinazolinone.

#### Method C. Indolization in Polyphosphoric Acid.

Hydrazone tetrahydropyrido[2,1-*b*]quinazolinone (**2**) (1 g) or its hydrochloride salt (1 g) was added to polyphosphoric acid (10 g) at 160-180°, and the reaction mixture was stirred for 20-30 minutes. The pH of the cooled, diluted (with 40 ml of water) reaction mixture was adjusted to 5 with 25% aqueous ammonia solution. The precipitated crystals were filtered off, dried and recrystallized to give the indolopyridoquinazolinone.

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