Nitrogen Bridgehead Compounds. Part 72 [1]. Straightforward Synthesis of 1,2,3,4-Tetrahydrorutaecarpine and Derivatives

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In polyphosphoric acid, the Fischer indolization of 6-arylhydrazono-1,2,3,4,6,7,8,9-octahydro-11*H*-pyrido-[2,1-*b*]quinazolin-11-ones, obtained from 1,2,3,4,6,7,8,9-octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones by three pathways, afforded substituted 1,2,3,4,7,8-hexahydro-5*H*-13*H*-indolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5-ones in high yields. The structures of the 6-substituted octahydropyridoquinazolinones and hexahydroindolopyridoquinazolinones were characterized by uv, ^1H and ^{13}C nmr data.

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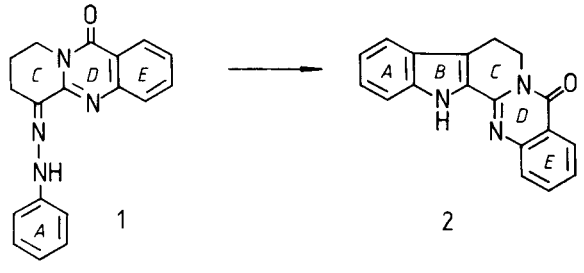
The pharmacological investigations of rutaecarpine alkaloid (**2**), known as an ingredient of the Chinese folk medicines Wu-Chu-Yu and Shih-Hu [2] (both prepared from the fruit of *Evodia rutaecarpa*), indicated that the derivatives of this pentacyclic nitrogen bridgehead ring system are worthy of consideration as diuretic, uterotonic and/or blood pressure influencing agents [3]. As the very low solubilities of these derivatives render pharmacological and biochemical investigations rather difficult, we set out to synthethize 1,2,3,4-tetrahydro derivatives of this ring system, hoping for an improvement in the lipophilicities.

Instead of the widely-used synthetic method for the preparation of rutaecarpine derivatives, which starts from tryptamine and its dervatives and in which rings C and D are connected in the last step [4], we chose the straightforward Fischer indolization of 6-hydrazono-1,2,3,4,6,7,8,9-octahydro-11*H*-pyrido[2,1-*b*]quinazolinones [5]. By means



of the latter possibility, facile total syntheses of rutaecarpine (**2**) [5] and derivatives substituted in ring A were recently reported [6], starting from 2-aminopyridine *via* 6-hydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**1**).

In these processes, rings B and C are joined in the last step.

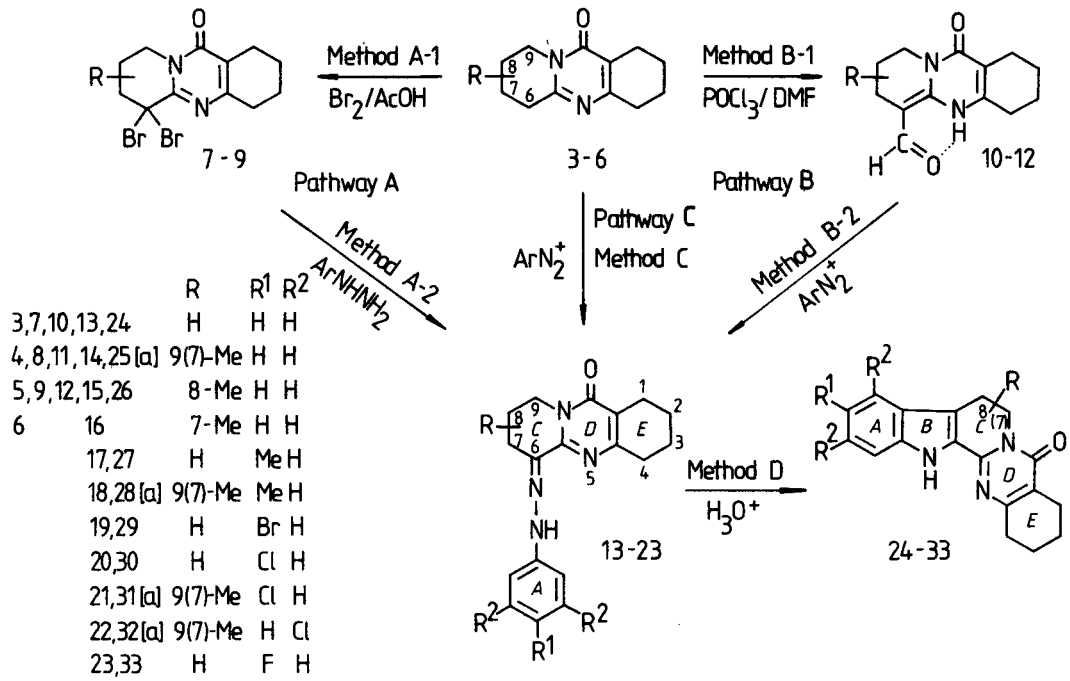
The synthesis of 6-hydrazonopyrido[2,1-*b*]quinazolinones is based on the fact that 6,7,8,9-tetrahydropyrido-[2,1-*b*]quinazolinone contains an active methylene group in position 6 [7]. As the latter is about 25 times more reactive than the reactive methylene groups in 1,2,3,4,6,7,8,9-octahydropyrido[2,1-*b*]quinazolinones, three reaction pathways were studied for the synthesis of 6-hydrazonooctahydropyrido[2,1-*b*]quinazolinones. Pathway A: bromination of 1,2,3,4,6,7,8,9-octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones and reaction of the dibromo derivatives with phenylhydrazine. Pathway B: introduction of a formyl group into position 6 by Vilsmeier-Haack formylation, followed by the Japp-Klingeman reaction of the formyl derivatives. Pathway C: direct diazonium coupling of the active methylene group of octahydropyrido[2,1-*b*]quinazolinones (Scheme 1).

The starting octahydropyridopyrimidinones **3-6** could be obtained in a two-step synthesis from 2-aminopyridines and ethyl 2-oxocyclohexanecarboxylate, and the resulting tetrahydropyrido[2,1-*b*]quinazolinones were hydrogenated [8].

Synthesis of 6-Hydrazonooctahydropyrido[2,1-*b*]quinazolinones **13-23**.

Pathway A.

Bromination of octahydropyrido[2,1-*b*]quinazolinones **3-5** in 75% acetic acid with bromine in the presence of sodium acetate at 50° yielded dibromo derivatives **7-9** in only 18-20% yields (Method A-1). Reaction of the dibromo derivative **7** with phenylhydrazine afforded the respective 6-(phenylhydrazono)octahydropyridoquinazolinone **13** in 52% yield (Method A-2).



	R	R^1	R^2
3,7,10,13,24	H	H	H
4,8,11,14,25[a]	9(7)-Me	H	H
5,9,12,15,26	8-Me	H	H
6 16	7-Me	H	H
17,27	H	Me	H
18,28[a]	9(7)-Me	Me	H
19,29	H	Br	H
20,30	H	Cl	H
21,31[a]	9(7)-Me	Cl	H
22,32[a]	9(7)-Me	H	Cl
23,33	H	F	H

[a] Me group is in position (7)

Scheme 1

Pathway B.

Vilsmeier-Haack acylation of octahydropyridopyrimidinones **3-5** was carried out with a complex of phosphoryl chloride and dimethylformamide [9]. The primarily formed 6-(dimethylamino)methylene derivatives were spontaneously hydrolyzed during the work-up process, to give 6-formyl derivatives **10-12**, which were isolated in 52-63% yields (Method B-1).

The Japp-Klingeman reaction [10] of 6-formyloctahydro-[2,1-*b*]quinazolinone **11** with phenyldiazonium chloride afforded the expected 6-(phenylhydrazono)octahydropyrido-[2,1-*b*]quinazolinone **14** in 73% yield (Method B-2).

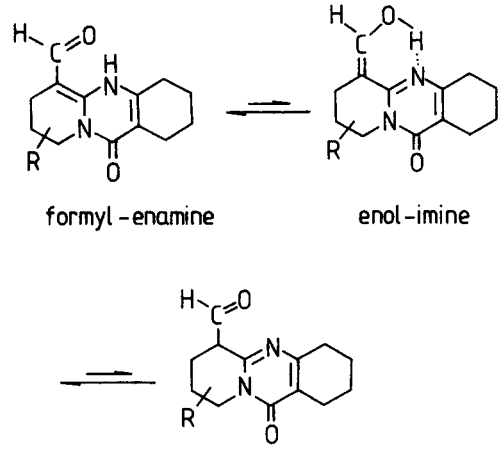
Pathway C:

In general, the best yields were obtained in the direct diazonium coupling reaction between octahydropyrimido-[2,1-*b*]quinazolinones **3-6** and aryldiazonium chlorides in 75% acetic acid (Method C) (Table 1).

The Structures of 9-Substituted Octahydro-11*H*-pyrido-[2,1-*b*]quinazolin-11-ones.

The structures of 6-substituted octahydro-11*H*-pyrido-quinazolinones **10**, **11** and **13-16** were investigated by ^1H and ^{13}C nmr. Physical, analytical and nmr data are tabulated in Tables 1, 2 and 3, and the substituent chemical shifts (SCS) of the methyl group in compounds **13-16** are given in Table 4.

On the basis of earlier investigations of similar nitrogen bridgehead compounds [9,11,12], three tautomeric forms have to be taken into consideration for the structures of formyl derivatives **10-12** (Scheme 2).



Scheme 2

The spectra of formyl derivatives **10** and **11** each contain only one set of signals. The broad signal of the N(1)H proton above 14 ppm indicates that the formyl-enamine tautomer, containing an intramolecular hydrogen-bond between N(1)H and the oxygen atom of the formyl group,

Table 1

Physical and Analytical Data on 6-Substituted 1,2,3,4,6,7,8-Octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **7-23**

Compound [a] No.	Method	Yield	Mp, °C (Solvent)	Formula (Molecular Weight)	Analysis % Calcd./Found C	H	N	Hlg
7	A-1	18.5	145 (EtOAc)	$C_{12}H_{14}Br_2N_2O$ (362.075)	39.81 39.95	3.90 3.85	7.73 7.67	44.14 44.30
8	A-1	20.0	125-127 (EtOAc)	$C_{13}H_{16}Br_2N_2O$ (376.102)	41.51 41.38	4.29 4.37	7.45 7.53	42.49 42.28
9	A-1	18.6	151-155 (EtOAc)	$C_{13}H_{16}Br_2N_2O$ (376.102)	41.51 41.38	4.29 4.31	7.45 7.50	42.49 42.55
10	B-1	63.0	160-161 (EtOAc)	$C_{13}H_{16}N_2O_2$ (232.284)	67.22 67.12	6.94 7.11	12.06 12.03	
11	B-1	74.0	140 (EtOAc)	$C_{14}H_{18}N_2O_2$ (246.311)	68.27 68.31	7.36 7.25	11.37 11.41	
12	B-1	52.0	119-120 (EtOAc)	$C_{14}H_{18}N_2O_2$ (246.311)	68.27 68.20	7.36 7.41	11.37 11.30	
13	A-2	52.0	212-213 (EtOH)	$C_{18}H_{20}N_4O$ (308.386)	70.11 69.93	6.53 6.51	18.17 18.07	
	C	85.0	210-212 (EtOH)					
14	B-2	73.0	242-244 [b] (EtOH)	$C_{19}H_{23}ClN_4O$ (358.874)	63.59 63.21	6.46 6.28	15.61 15.75	9.88 9.65
	C	83.0	190-193 (EtOH)	$C_{19}H_{22}N_4O$ (322.413)	70.78 70.55	6.87 6.91	17.37 17.27	
15	C	59.0	219 (EtOH)	$C_{19}H_{22}N_4O$ (322.413)	70.78 70.83	6.87 6.82	17.37 17.40	
16	C	59.0	186-188 (EtOH)	$C_{19}H_{22}N_4O$ (322.413)	70.78 70.91	6.87 6.75	17.37 17.45	
17	C	46.0	203-204 (EtOH)	$C_{19}H_{22}N_4O$ (322.413)	70.78 70.63	6.87 6.56	17.37 17.17	
18	C	74.0	187-188 (EtOH)	$C_{20}H_{24}N_4O$ (336.440)	71.40 71.17	7.19 6.96	16.65 16.72	
19	C	65.1	199-201 (EtOH)	$C_{18}H_{19}BrN_4O$ (387.287)	55.82 56.03	4.94 4.87	14.96 14.50	20.63 20.71
20	C	73.0	220 (EtOH)	$C_{18}H_{19}ClN_4O$ (342.831)	63.06 63.24	5.59 5.51	16.34 16.32	
21	C	70.2	207-208 (EtOH)	$C_{19}H_{21}ClN_4O$ (356.858)	63.95 64.14	5.93 6.17	15.70 15.78	
22	C	33.0	227-228 (EtOH)	$C_{19}H_{20}Cl_2N_2O$ (391.303)	55.33 58.40	5.15 5.23	14.31 14.27	
23	C	74.2	233-235 (EtOH)	$C_{18}H_{19}FN_4O$ (326.377)	66.24 66.36	5.87 5.80	17.16 17.15	5.82 5.80

[a] Substituents for specific compounds are given in Scheme 1. [b] Hydrochloride.

is predominant. The signal of the formyl group appears at relatively high field, at 8.58 and 8.77 ppm, which points to a mobile tautomeric equilibrium between the formyl-enamine and enol-imine tautomers.

When the ^{13}C chemical shifts of the carbons of the formyl derivatives are compared with those of the respective carbons of 9-formyl-1,6,7,8-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones [12], further strong evidence is obtained of a mobile formyl-enamine and enol-imine equilibrium, with the predominance of the former.

Table 2

Characteristic ^{1}H NMR Data on 6-Substituted 11*H*-Pyrido[2,1-*b*]quinazolin-11-ones **10**, **11**, **13-16** in Deuteriochloroform (δ = 0 ppm)

Compound No.	H-9$_{ax}$	H-9$_{eq}$	Me	N(1)H	=N-NH	CHO	Coupling Constants (Hz)
10	3.75 - 4.10 m			14.59 br		8.58 s	
11		4.94 m	1.22 d	14.60 br		8.77 s	
13 [a]	3.75 - 4.10 m				14.32 br		
14 [a]		5.01 m	1.30 d		14.49 br		
15 [a]	3.24 dd	4.35 ddd	1.10 d		14.34 br		$^2J_{9e,9a}$ = 14.2, $^3J_{8a,9a}$ = 3.9, $^3J_{8a,9a}$ = 9.8
16 [a]			1.29 d		14.38 br		$^2J_{9e,9a}$ = 14.5, $^3J_{8e,9a}$ = 4.6, $^3J_{8e,9e}$ = 4.8, $^3J_{8a,9e}$ = 6.0, $^3J_{8a,9a}$ = 8.7, $^3J_{7a,8e}$ = 5.2, $^3J_{7a,8a}$ = 8.7

[a] *Z* isomer. br = broad singlet, s = singlet, d = doublet, m = multiplet.

Table 3

^{13}C Chemical Shifts on 6-Substituted 11*H*-Pyrido[2,1-*b*]quinazolin-11-ones **10**, **11**, **13-16** in Deuteriochloroform (δ = 0 ppm)

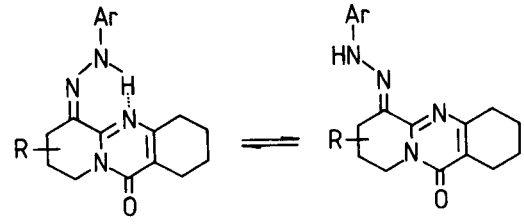
Compound No.	C(1)	C(2)	C(3)	C(4)	C(4a)	C(5a)	C(6)	C(7)	C(8)	C(9)	C(11)	C(11a)	Me	Substituents at position 6			
10	21.2 [a]	21.3 [a]	21.3 [a]	27.4	154.5	148.2	90.8	22.2	20.5	41.3	160.4	111.5		178.5			
11	21.3 [a]	21.0 [a]	21.1 [a]	26.8	150.1	147.0	88.6	17.5	25.4	45.2	159.8	110.8	17.1	181.2			
13 [b]	22.9 [a]	22.4 [a]	22.0 [a]	31.5	156.9	148.5	124.1	31.1	21.7	43.1	162.0	120.6		144.3	113.8	129.6	121.7
14 [b]	22.6 [a]	22.2 [a]	21.8 [a]	31.6	156.8	148.0	123.8 [c]	26.0 [d]	27.2	47.0	161.3	120.8	18.5 [e]	144.3	113.9	129.6	121.8
15 [b]	22.9 [a]	22.4 [a]	22.1 [a]	31.5	156.8	[f]	124.1	39.1	27.5	49.1	162.0	120.6	18.4	144.3	113.8	129.6	121.7
16 [b]	23.0 [a]	22.5 [a]	22.2 [a]	31.3	156.5	148.1	127.6	34.4	29.0	41.0	161.4	120.0	18.8	144.2	113.4	129.2	121.3

[a] Interchangeable within each row. [b] *Z* isomer. [c] 129.2 ppm in *E* isomer. [d] 20.0 ppm in *E* isomer. [e] 17.2 ppm in *E* isomer. [f] Could not be assigned because of low intensity.

Table 4

SCS Values (ppm) of Methyl Groups in *Z* Isomers of 6-Hydrazonooctahydropyridoquinazolinones **14-16**

Compound No.	α	β	γ
14	3.9 (at C-9)	5.5 (at C-8)	−5.1 (at C-7)
15	5.8 (at C-8)	8.0 (at C-7 and 6.0 (at C-9)	
16	3.3 (at C-7)	7.3 (at C-8)	−2.1 (at C-9)



E *Z*

Scheme 3

Table 5

Proportions of *Z* Isomers of 6-Phenylhydrazonooctahydropyridoquinazolinones at Equilibrium

Compound No.	In Deuteriochloroform %	In DMSO-d$_6$ %
13	100	80
14	95	70
15	100	90
16	100	100

Earlier investigations of 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [13] and 6-arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones [14] suggested that *E*-*Z* geometric isomers can be considered for the structures of hydrazonopyridoquinazolinones **13-23** (Scheme 3). The interconversion of the *Z* and *E* isomers requires low activation energies, as equilibrium mixtures were obtained in either deuteriochloroform or DMSO-d$_6$ immediately after dissolution of hydrazones **13-16**.

Table 6

Physical and Analytical Data on 1,2,3,4,7,8-Hexahydro-5*H*-13*H*-indolo[2',3',3,4]pyrido[2,1-*b*]quinazolin-5-ones

Compound [a] No.	Method	Reaction period minutes	Reaction temp °C	Yield %	Mp °C (solvent)	Formula (Molecular Weight)	Analysis % Calcd./Found C	H	N	Hlg
24	D-1	30	180	93	259-262 (EtOAc)	$C_{18}H_{17}N_3O$ (291.351)	74.20 74.08	5.88 5.84	14.42 14.48	
	D-2	30	200	51	258-260 (EtOAc)					
25	D-1	20	180	42	232 (EtOH)	$C_{19}H_{19}N_3O$ (305.378)	74.72 74.66	6.27 6.28	13.75 13.83	
26	D-1	40	180	63	220-221 (EtOAc)	$C_{19}H_{19}N_3O$ (305.378)	74.72 74.77	6.27 6.31	13.75 13.67	
27	D-1	40	180	42	222-224 (EtOAc)	$C_{19}H_{19}N_3O$ (305.378)	74.72 74.76	6.27 6.24	13.89 13.89	
28	D-1	40	180	42	220 (EtOAc)	$C_{20}H_{21}N_3O$ (319.405)	75.20 75.11	6.62 6.70	13.15 13.22	
29	D-1	20	170	55	247 (*i*-PrOH)	$C_{18}H_{16}BrN_3O$ (370.247)	58.39 58.42	4.35 4.23	11.34 11.20	21.58 21.47
30	D-1	30	180	74	288-290 (EtOAc)	$C_{18}H_{16}ClN_3O$ (325.796)	66.35 66.28	4.94 4.90	12.89 12.95	10.88 10.81
31	D-1	30	180	73	248 (EtOH)	$C_{19}H_{18}ClN_3O$ (339.823)	67.15 67.08	5.33 5.37	12.36 12.41	10.43 10.35
32	D-1	50	190	72	296-297 (EtOAc)	$C_{19}H_{17}Cl_2N_3O$ (374.268)	60.97 60.82	4.57 4.55	11.22 11.10	18.94 19.08
33	D-1	50	175	61	302-305 (*i*-PrOH)	$C_{18}H_{16}FN_3O$ (309.341)	69.89 70.00	5.21 5.18	13.58 13.55	

[a] Substituents in specific compounds are given in the Scheme.

Table 7

UV Data on Octahydro-5*H*,11*H*-indolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5-ones **24-28** and **30-32** in Ethanol

Compound No.	R	R¹	R²	λ max (nm) (log ε)						
24	H	H	H	360 (4.31)	345 (4.46)	334 (4.41)		248 (4.17)		209 (4.53)
25	7-Me	H	H	363	346	334		254	248	210
26	8-Me	H	H	360 (4.29)	345 (4.44)	334 (4.39)	281 (3.67)	253 (4.02)	247 (4.03)	209 (4.52)
27	H	Me	H	361 (4.05)	347 (4.15)	336 (4.09)		252 (3.89)		209 (4.17)
28	7-Me	Me	H	362	349	336		255		211
30	H	Cl	H	361 (4.32)	345 (4.48)	334 (4.41)		256 (4.12)		212 (4.50)
31	7-Me	Cl	H	362 (4.15)	346 (4.30)	336 (4.23)	256 (3.97)	251 (3.97)		213 (4.34)
32	H	H	Cl	367 (3.96)	349 (4.12)	335 (4.05)	259 (3.86)	253 (3.85)	243 (3.90)	213 (4.06)

The ratios of the *E* and *Z* isomers were determined from the intensities of the NH group signals in deuteriochloroform and DMSO-d_6 (Table 5). The predominance of the sterically more crowded *Z* isomer can be explained by the gain in energy due to the formation of an internal hydrogen-bond between ring atom N(5) and NH group. When a methyl group is present at position 7 (compound **16**), both *E* and *Z* isomers are sterically crowded, and thus only the *Z* isomer can be detected in either deuteriochloroform or DMSO-d_6.

Table 8

^{1}H NMR Data on Hexahydro-5*H*,11*H*-Indolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5-ones **24-26**, **30** and **32** (δ = 0 ppm)

Compound No.	Me	2- and 3-H_2	1- and 4-H_2	H-7	H-8	Ar-H	NH	Solvent
24		1.62 m	2.60 m	4.46 t	3.15 t	6.87-7.65 m	9.62 s	$CDCl_3$
25	1.31 d	1.75 m	2.60 m	5.52 m	3.18 d	7.00-7.70 m	9.84 s	$CDCl_3$
26	1.42 d	1.77 m	2.60 m	4.40 m	3.54 m	6.90-7.70 m	10.30 s	$CDCl_3$ + DMSO-d_6
30		1.76 m	2.58 m	4.45 t	3.10 t	6.90-7.52 m	9.49 s	$CDCl_3$
32	1.20 d	1.78 m	2.61 m	5.30 m	3.25 d	7.32 d, 7.10 d	12.20 s	DMSO-d_6

The methyl group at position 9 (in compounds **11** and **14**) occupies a quasi-axial position, due to the 1-3 allyl-type strain [15,16] which would develop between the methyl group and the neighboring carbonyl group if the methyl group were in a quasi-equatorial position.

Fischer Indolization.

Fischer indolization [17] of hydrazone **13** was unsuccessful when this compound was heated in ethanol or acetic acid in the presence of hydrogen chloride, or in formic acid. Polyphosphoric acid (Method D-1) proved to be a more useful cyclizing agent than zinc chloride (Method D-2), and therefore the further hydrazones **14**, **15** and **17-23** were transformed into pentacyclic derivatives **25-33** by heating in polyphosphoric aicd (Table 6).

The uv and ^{1}H nmr data on some hexahydro-5*H*,11*H*-indolo[2',3':3,4]pyrido[2',1-*b*]quinazolin-5-ones are listed in Tables 7 and 8. In compounds **25** and **32** the methyl group at position 7 occupies a quasi-axial position. This is indicated by the downfield shift of H-7 due to the anisotropy of the neighbouring carbonyl group [16].

The saturation of ring E of rutaecarpine and the introduction of different substituents into rings A and C do not lead to significantly improved solubilities and lipophilicities of the resulting compounds **24-33**.

EXPERIMENTAL

Melting points are uncorrected. The uv spectra were recorded on a UNICAM SP-800 spectrophotometer, and ^{1}H and ^{13}C nmr spectra on a Brucker WP-80Ft spectrometer at 80 and 20.1 MHz, respectively, with tetramethylsilane as internal standard.

Solvents for recrystallization, and the yields and melting points of the products are given in Tables 1 and 6.

Bromination. Method A-1.

To a solution of octahydropyrido[2,1-*b*]quinazolinone **3-5** (10 mmoles) in 75% acetic acid (16 ml) in the presence of sodium acetate (2.46 g, 30 mmoles), solution of bromine (3.2 g, 20 mmoles) in 75% acetic acid (16 ml) was added dropwise at 50°. After the addition of bromine, the mixture was stirred for 1.5 hours and the reaction mixture was then diluted with water (200 ml). The precipitated crystals were collected by filtration and were suspended in warm ethanol. 6,6-Dibromooctahydropyrido-[2,1-*b*]quinazolinone **7** or **9** was filtered off, washed with ethanol, dried and recrystallized.

In the case of the 9-methyl derivative **8**, the aqueous solution was extracted with chloroform (3 × 30 ml). The dried (sodium sulphate) chloroform was evaporated to dryness *in vacuo*. The oily residue was crystallized from ethyl acetate to give compound **8**.

Method A-2.

6,6-Dibromooctahydropyrido[2,1-*b*]quinazolinone **7** (1.81 g, 5 mmoles) was reacted with phenylhydrazine (2 g, 20 mmoles) in refluxing ethanol for 4 hours. The reaction mixture was cooled to ambient temperature, and was then left to crystallize in a refrigerator overnight. The precipitated crystals were filtered off, and subsequently treated with 10% aqueous sodium acetate solution (20 ml). The yellow hydrazono derivative **13** was filtered off, dried and recrystallized.

Vilsmeier-Haack Formylation. Method B-1.

To a cooled solution of octahydropyrido[2,1-*b*]quinazolinone **3-5** (10 mmoles) in dimethylformamide (100 ml), phosphoryl chloride (3.07 g, 20 mmoles) was added dropwise at 20-25°. The reaction mixture was stirred at ambient temperature for 0.5 hour, at 60° for 1 hour, and then at 95° for 0.5 hour. The cooled reaction mixture was poured onto crushed ice (30 g) and the *p*H of the aqueous mixture was adjusted to 7 with 20% aqueous sodium carbonate solution. The reaction mixture was kept at 25° for 2 hours. The precipitated crystals were filtered off and washed with water.

In the case of formyl derivatives **10** and **12**, the product was first purified by column chromatography on silica gel (Merck) with gradient elution using benzene-methanol.

The formyl derivative **10-12** was recrystallized from ethyl acetate (see Table 1).

Japp-Klingeman Reaction. Method B-2.

Aryldiazonium chlorides were prepared by the usual procedure [18] from aromatic amines (10 mmoles) in 20% hydrochloric acid (5 ml) at −5° with a solution of sodium nitrite (0.69 g, 10 mmoles) in water (5 ml). After stirring for 0.5 hour, the reaction mixture was diluted with acetic acid (5 ml) and the *p*H of the solution was adjusted to 4 with sodium acetate (3.3 g).

To a solution of the aryldiazonium chloride, a solution of 6-formyloctahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one **11** (10 mmoles) in 75% acetic acid (30 ml) was added dropwise at 0°. The mixture was stirred at 0° for 3 hours and allowed to stand overnight in a refrigerator. After dilution of the reaction mixture with water (30 ml), the precipitated hydrazono hydrochloride **14**. HCl was filtered off, washed with water and dried (see Table 1).

Method C.

To a solution of the aryldiazonium chloride, a solution of the requisite

octahydro-11*H*-pyrido[2,1-*b*]quinazolinone **3-6** (10 mmoles) in 50% acetic acid (10 ml) was added dropwise at 0°. The mixture was stirred at between −5° and 0° for 3 hours and allowed to stand overnight in a refrigerator. The precipitated crystalline hydrazono compound **13-23** was filtered off, washed with water, dried and refluxed with ethanol (see Table 1).

Indolization in Polyphosphoric Acid. Method D-1.

Hydrazonooctahydropyrido[2,1-*b*]quinazolinone **13-15** or **17-23** (1 g) was added to polyphosphoric acid (Fluka) (10 g) at the temperature indicated in Table 6, and the reaction mixture was stirred for 20-50 minutes. The cooled reaction mixture was treated with water (50 ml), and the *p*H of the aqueous reaction mixture was then adjusted to 5 with 25% aqueous ammonia solution. In the preparation of compounds **24**, **25**, **31** and **32**, the precipitated crystals were filtered off, dried and recrystallized. In the preparation of compounds **26**, **27**, **28**, **30** and **33**, the aqueous reaction mixture was extracted with chloroform (3 × 20 ml). The combined organic phase was clarified with active carbon. The dried (sodium sulphate) chloroform solution was evaporated to dryness *in vacuo*, and the residue was recrystallized.

In the preparation of bromo derivative **29**, the chloroform solution was chromatographed on a Kieselgel column with ethyl acetate as eluent.

Indolization with Zinc Chloride. Method D-2.

A mixture of hydrazonooctahydropyrido[2,1-*b*]quinazolinone **13** (1 g) and anhydrous zinc chloride (5 g) was heated at 200° for 30 minutes. The cooled dark reaction mixture was treated with water (50 ml). The precipitated crystals were filtered off and washed with water. The crystals were dissolved in chloroform and the organic solution was clarified with active carbon. The dried (sodium sulphate) solution was evaporated. The residue was recrystallized from ethyl acetate to give the hexahydroindolopyridoquinazolinone **24**.

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