Nitrogen Bridgehead Compounds. Part 45 [1]. Synthesis of 6-Arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido-[2,1-*b*]quinazolin-11-ones

József Kökösi, István Hermecz* [a], Benjámin Podányi [a], György Szász, and Zoltan Mészáros [a]

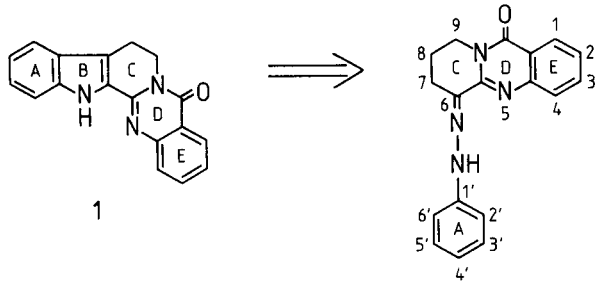
Institute for Pharmaceutical Chemistry of the Semelweis Medical University, H-1092 Budapest, Hőgyes E. u. 7, Hungary
[a] CHINOIN Pharmaceutical and Chemical Works Ltd., H-1045 Budapest, Tó u. 1-5, Hungary

Received January 20, 1984

A series of 6-arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **3-37**, conveneint starting materials for indolopyridoquinazolines, were prepared by diazonium coupling between aryldiazonium chlorides and 6,7,8,9-tetrahydro- **2**, 6-formyl-5,7,8,9-tetrahydro- **39**, 6-(dimethylamino)methylene-6,7,8,9- **38** or 6-carboxyl-5,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **43**. The arylhydrazono derivatives were also prepared from 6-bromo- **45** or 6,6-dibromo-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolines **46** with arylhydrazines. The structures of the 6-arylhydrazonopyridoquinazolines were characterized by uv and ^{1}H nmr spectroscopy. The 6-arylhydrazono derivatives show a solvent-dependent *E-Z* isomerism.

J. Heterocyclic Chem., **21**, 1301 (1984).

We recently described a facile total synthesis [2] of rutecarpine, an alkaloid having an indolopyridoquinazoline skeleton. The key step of this synthesis was the Fischer-indole cyclization of a phenylhydrazonopyridoquinazoline derived from rutecarpine using the retrosynthetic approach (Scheme 1).



1

Scheme 1

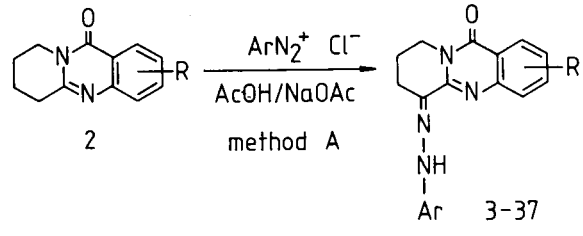
Rutecarpine is a component of several Chinese ethnic medicines [3a,b]. Alkaloids with an indolopyridoquinazoline skeleton are noted for their cardiovascular, diuretic and uterotonic effects [3c], while pyrido[2,1-*b*]quinazolines deserve interest for their antiasthmatic activity [4].

Generalization of the synthetic scheme used for the preparation of rutecarpine may provide a convenient route for the preparation of new pyrido[2,1-*b*]quinazolines and rutecarpine analogues too. Appropriate choice of the substituents attached to the phenyl ring leads to variation in the substitution of ring **A**, while the various substituents on the pyrido[2,1-*b*]quinazoline yield differently substituted rings **C** and **E**.

In this paper, methods elaborated for the preparation of 6-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[2,1-*b*]quinazolin-11-ones **3-37** are reported. The starting materials, substituted pyrido[2,1-*b*]quinazolines **2**, were prepared by methods described in the literature [5-7].

Synthesis.

In the preparation of the arylhydrazones **3-37** we exploited the reactivity of the active 6-methylene group in 6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-ones **2** towards electrophilic reagents [8,9]. This permitted the direct diazonium coupling of the pyridoquinazolines **2**, which proved to be the most simple means of preparation of arylhydrazones. The reaction was carried out in acetic acid in the presence of sodium acetate at *p*H 4-5 (Method A in Scheme 2) and gave high yields.



2 method A 3-37

Scheme 2

Diazonium coupling could be performed under the same conditions with phenyldiazonium compounds containing both electron-attracting and electron-releasing substituents, as well as with diazonium salts of condensed aromatic (naphthyl) and heteroaromatic (3-pyridyl, 4-antipyrinyl) compounds. The products crystallized directly from the reaction mixture (Method A-1). The arylhydrazones were sometimes isolated as the hydrochloride salts, from which the free base was liberated in a separate step (Method A-2). The compounds thus prepared are listed in

Table 1

Preparation of 6-Arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones by Method A

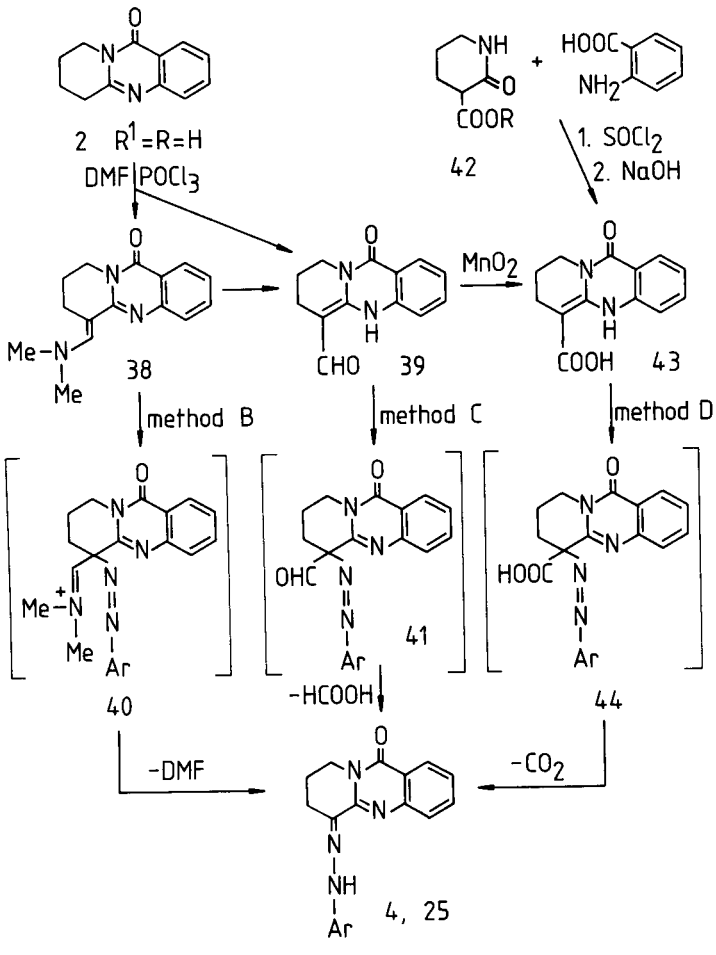
Compound No.	Ar	R	Method	Yield %	Mp (°C)	Molecular formula	Analyses (%) Calculated C	H	N	Found C	H	N
3	Ph	2-NO_2	A-1	81	247-248	$C_{18}H_{16}N_4O$	71.03	5.29	18.41	70.97	5.27	18.25
5	4-HO-Ph	H	A-2	81	247-248	$C_{18}H_{16}N_4O_2$	67.48	5.03	17.48	67.52	5.08	17.44
6	4-MeO-Ph	H	A-2	92	215	$C_{19}H_{18}N_4O_2$	68.24	5.42	16.75	68.20	5.44	16.83
7	1-naphthyl	H	A-1	86	192-193	$C_{22}H_{16}N_4O$	70.57	4.84	14.96	70.55	4.84	14.40
8	4-NO_2-Ph	H	A-1	83	250	$C_{18}H_{15}N_5O_3$	61.88	4.32	20.04	61.47	4.30	20.12
9	Ph	2-COOMe	A-1	92	230-232	$C_{20}H_{18}N_4O_3$	66.28	5.00	15.46	66.34	5.05	15.40
10	Ph	2-COOEt	A-1	90	223-225	$C_{21}H_{20}N_4O_3$	67.00	5.35	14.88	66.88	5.41	14.92
11	4-Ph-Ph	H	A-1	89	198-199	$C_{24}H_{20}N_4O$	75.77	5.29	14.72	75.82	5.31	14.66
12	4-antipyrinyl	H	A-1	53	211	$C_{23}H_{22}N_6O_2$	66.65	5.35	20.27	66.23	5.42	20.33
13	4-Me-Ph	2-Cl	A-1	64	231	$C_{19}H_{17}N_4OCl$	58.72	4.65	14.42	58.88	4.78	15.18
14	Ph	2-COOH	A-1	98	340	$C_{19}H_{16}N_4O_3$	65.51	4.62	16.08	65.38	4.70	16.03
15	2-naphthyl	H	A-1	96	220	$C_{22}H_{18}N_4O$	70.57	4.84	14.96	70.33	4.65	14.87
16	4-Me-Ph	H	A-1	88	187-188	$C_{19}H_{18}N_4O$	71.67	5.69	17.59	72.13	5.60	17.48
17	4-PhO-Ph	H	A-1	83	178-179	$C_{24}H_{20}N_4O_2$	72.71	5.08	14.13	72.50	4.96	14.07
18	4-MeCO-Ph	H	A-1	81	255	$C_{20}H_{18}N_4O_2$	69.34	5.23	16.17	69.33	5.35	16.28
19	Ph	2,3,4-$(OMe)_3$	A-1	77	187-189	$C_{21}H_{22}N_4O_4$	63.54	5.62	14.20	63.87	5.60	14.15
20	Ph	3-COOEt	A-1	85	197-201	$C_{21}H_{20}N_4O_3$	60.70	5.35	14.88	60.66	5.38	14.89
21	Ph	2-Cl	A-1	65	219-222	$C_{18}H_{15}N_4OCl$	63.81	4.46	16.53	63.84	4.56	16.71
22	4-Cl-Ph	2-Cl	A-1	64	227	$C_{18}H_{14}N_4OCl_2$	58.08	3.79	15.05	58.04	3.73	14.72
23	Ph	2,3-OCH_2O-	A-1	93	226	$C_{19}H_{16}N_4O_3$	65.50	4.62	16.08	65.54	4.67	16.07
24	2,6-Me_2-Ph	H	A-1	78	146-149	$C_{20}H_{20}N_4O$	72.26	6.06	16.85	72.18	6.08	16.92
25	Ph	H	A-1	94	182-184	$C_{18}H_{16}N_4O$	71.03	5.29	18.41	70.97	5.27	18.25
26	4-F-Ph	H	A-2	90	219-221	$C_{18}H_{15}N_4OF$	67.07	4.69	17.38	67.01	4.71	17.40
27	Ph	2,3-$(OMe)_2$	A-1	60	225	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.37	65.72	5.26	15.21
28	4-Cl-Ph	H	A-1	94	191-192	$C_{18}H_{15}N_4OCl$	63.81	4.46	16.53	64.01	4.57	16.25
29	4-Br-Ph	H	A-1	84	180-183	$C_{18}H_{15}N_4OBr$	56.41	3.94	14.61	56.24	3.85	14.51
30	4-HOOC-Ph	H	A-2	91	298	$C_{19}H_{16}N_4O_3$	65.50	4.62	16.08	65.46	4.66	16.12
31	4-EtOOC-Ph	H	A-1	92	214	$C_{21}H_{20}N_4O_3$	67.00	5.35	14.88	66.87	5.38	14.94
33	3-Cl-Ph	H	A-1	89	181-183	$C_{18}H_{15}N_4OCl$	63.81	4.46	16.53	63.95	4.58	16.65
34	3-CF_3-Ph	H	A-1	83	197	$C_{19}H_{15}N_4OF$	61.28	4.06	15.04	61.43	4.12	14.86
35	4-CN-Ph	H	A-2	82	217	$C_{19}H_{15}N_5O$	69.28	4.59	21.26	69.23	4.63	21.29
37	3-pyridyl	H	A-2	83	188	$C_{17}H_{15}N_5O$	66.87	4.95	22.93	66.78	4.99	22.97

Table 2

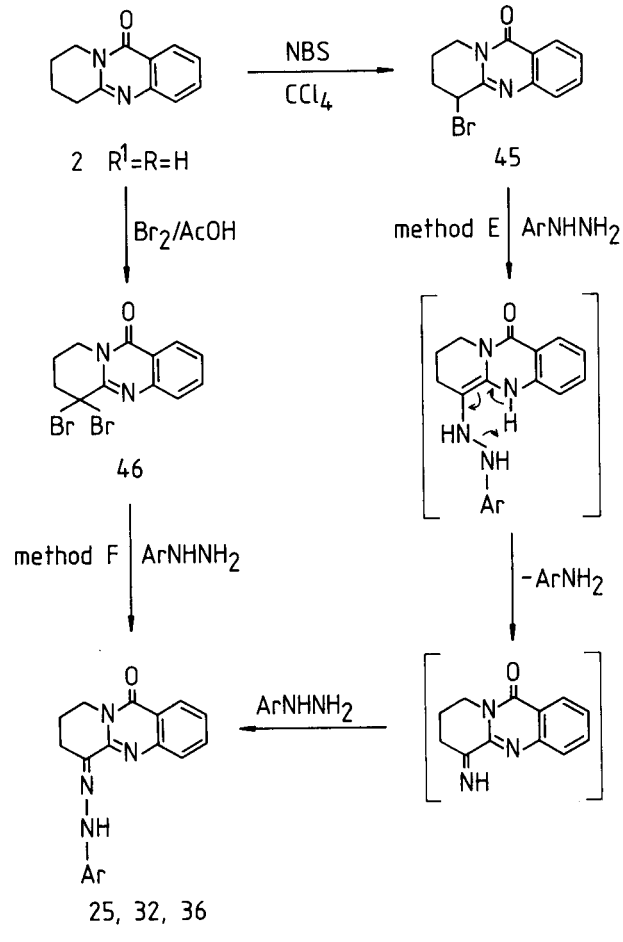
Preparation of 6-Arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones by Method B-F

Compound No.	Ar	R	Method	Yield %	Mp (°C)	Molecular formula	Analyses (%) Calculated C	H	N	Found C	H	N
25	Ph	H	B	98	181-183	$C_{18}H_{16}N_4O$	71.03	5.29	18.41	71.12	5.31	18.38
4	4-Me_2N-Ph	H	C	27	148-151	$C_{20}H_{21}N_5O_2$	69.14	6.09	20.15	69.08	6.12	20.25
25	Ph	H	C	95	180-182	$C_{18}H_{16}N_4O$	70.03	5.29	18.41	69.87	5.30	18.42
4	4-Me_2N-Ph	H	D	21	146-149	$C_{20}H_{21}N_5O$	69.14	6.09	20.15	69.10	6.10	20.16
25	Ph	H	D	85	182-184	$C_{18}H_{16}N_4O$	71.03	5.29	18.41	71.07	5.30	18.37
25	Ph	H	E	59	177-179	$C_{18}H_{16}N_4O$	71.03	5.29	18.41	71.00	5.27	18.33
32	Ph	9-Me	E	47	187-189	$C_{19}H_{18}N_4O$	71.67	5.69	17.59	71.62	5.68	17.62
25	Ph	H	E	80	179-181	$C_{18}H_{16}N_4O$	71.03	5.29	18.41	70.96	5.33	18.36
32	Ph	9-Me	F	75	189-191	$C_{19}H_{18}N_4O$	71.67	5.69	17.59	71.66	5.65	17.61
36	2-pyridyl	H	F	87	198-200	$C_{17}H_{15}N_5O$	66.87	4.95	22.93	66.78	4.99	22.97

Table 1. In certain cases direct diazonium coupling failed and therefore other methods had to be developed. For instance, diazonium salts containing a highly electron-releasing group (such as *p*-dialkylaminophenyl diazonium salts) did not enter into direct diazonium coupling. This could be circumvented in increasing the reactivity of the methylene group of the substrate **2**. Thus, by use of the Vilsmeier-Haack reagent, a formyl or a dimethylaminomethylene group was attached to C-6 of the pyridoquinazolinone **2** (R = R^1 = H) [8,9], followed by a Japp-Klingemann reaction (Methods B and C) to yield the desired 6-arylhydrazonopyridoquinazolinone (Scheme 3, Table 2). The



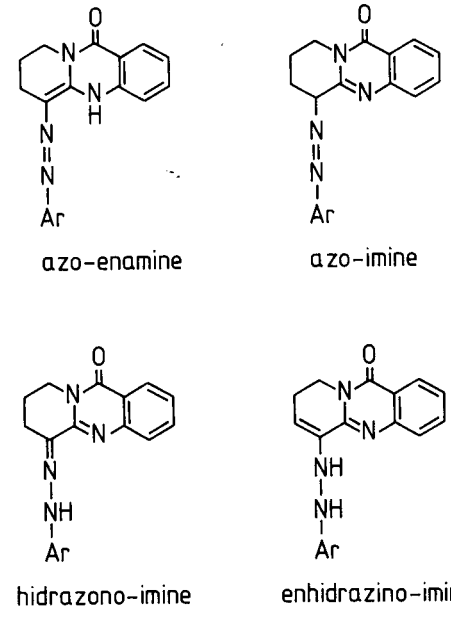
Scheme 3



Scheme 4

latter reaction was performed in aqueous dimethylformamide in the presence of sodium acetate. Diazonium coupling is accompanied by the spontaneous elimination of the activating groups. For activation, a carboxyl group can be used too (Method D). Pyridoquinazoline-6-carboxylic acid **43** can be prepared either by mild oxidation of the formyl compound **39** with manganese dioxide, or by condensing 3-carbethoxypiperidone **42** with anthranilic acid and hydrolysing the product [7]. Diazonium coupling of **43** is accompanied by decarboxylation and liberation of carbon dioxide.

The above-described methods can only be applied to aromatic or heteroaromatic amines which form stable aryldiazonium salts. If this is not the case, arylhydrazines can be used to prepare 6-arylhydrazonopyridoquinazolines. 6,7,8,9-Tetrahydro-11*H*-pyrido[2,1-*b*]quinazoline **2**, (R = R¹ = H) can be transformed with *N*-bromosuccinimide to the 6-bromo derivative **45**, and with bromine in acetic acid to the 6,6-dibromo derivative **46** [10,11]. Refluxing the bromo compounds with arylhydrazines in ethanol for 4-6 hours provides the 6-arylhydrazono derivatives **25, 32, 36** (Methods E and F in Scheme 4).



Scheme 5

Table 3

UV Spectra of 6-Arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **3-37**

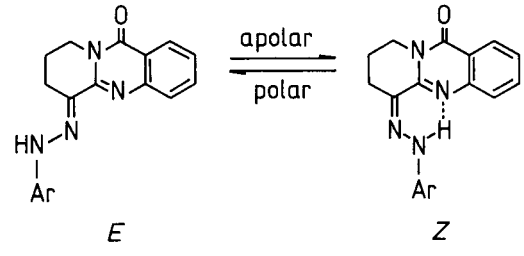
Compound No.	Ar	R	Absorption Maximum (nm) (log ε)				
3	Ph	2-NO_2	245 (4.34)	325 (4.16)	432 (4.46)		
4	4-Me_2N-Ph	H	232 (4.47)	256 (4.34)	308 (4.05)	421 (4.38)	
5	4-HO-Ph	H	231 (4.32)	255 (4.14)	304 (3.90)	417 (4.21)	
6	4-MeO-Ph	H	232 (4.33)	254 (4.20)	304 (4.23)	413 (4.29)	
7	1-naphthyl	H	248 (4.38)	310 (4.01)	410 (4.19)		
8	4-NO_2-Ph	H	227 (4.30)	314 (3.92)	408 (4.48)		
9	Ph	2-$COOCH_3$	215 (4.58)	248 (4.25)	290 (4.67)	300 (4.05)	408 (4.46)
10	Ph	2-$COOC_2H_5$	215 (4.59)	248 (4.26)	290 (4.08)	300 (4.08)	406 (4.46)
11	4-Ph-Ph	H	222 (4.35)	272 (4.25)	401 (4.57)		
12	4-antipyril	H	227 (4.38)	245i(4.18)	298 (4.00)	400 (4.10)	
13	4-Me-Ph	2-Cl	230 (4.32)	247 (4.20)	303 (3.92)	400 (4.32)	
14	Ph	2-COOH	213 (4.53)	248i(4.23)	301 (3.91)	398 (4.36)	
15	2-naphthyl	H	232 (4.58)	246 (4.41)	294 (4.09)	398 (4.38)	
16	4-Me-Ph	H	230 (4.34)	250 (4.26)	297 (3.91)	395 (4.29)	
17	4-PhO-Ph	H	232 (4.36)	257 (4.28)	300 (4.12)	394 (4.34)	
18	4-MeCO-Ph	H	227 (4.37)	300 (4.24)	392 (4.53)		
19	Ph	2,3,4-$(OMe)_3$	246 (4.60)	321 (3.83)	392 (4.10)		
20	Ph	3-$COOC_2H_5$	240 (4.68)	300 (4.01)	392 (4.47)		
21	Ph	2-Cl	230 (4.36)	248 (4.23)	298 (3.98)	391 (4.39)	
22	4-Cl-Ph	2-Cl	230 (4.35)	250 (4.18)	303 (4.00)	390 (4.20)	
23	Ph	2,3-O-CH_2O-	226i(4.32)	243 (4.50)	302 (3.71)	389 (4.30)	
24	2,6-Me_2-Ph	H	228i(4.28)	254 (4.18)	294 (3.89)	389 (4.20)	
25	Ph	H	231 (4.40)	250 (4.30)	296 (3.94)	388 (4.36)	
26	4-F-Ph	H	230 (4.26)	246 (4.07)	298 (3.85)	388 (4.17)	
27	Ph	2,3-$(OMe)_2$-	243 (4.52)	300 (3.86)	388 (4.38)		
28	4-Cl-Ph	H	230 (4.34)	256 (4.26)	300 (3.96)	387 (4.36)	
29	4-Br-Ph	H	230 (4.38)	256 (4.30)	300 (4.07)	386 (4.41)	
30	4-COOH-Ph	H	227 (4.26)	280 (4.14)	385 (4.40)		
31	4-$COOC_2H_5$-Ph	H	225 (4.24)	283 (4.19)	385 (4.39)		
32	Ph	9-Me	228 (4.36)	248 (4.26)	305 (3.96)	380 (4.33)	
33	3-Cl-Ph	H	230 (4.37)	252 (4.25)	300 (3.94)	380 (4.35)	
34	3-CF_3-Ph	H	227 (4.35)	253 (4.27)	298 (3.98)	379 (4.33)	
35	4-CN-Ph	H	227 (4.32)	275 (4.08)	378 (4.42)		
36	2-pyridyl	H	229 (4.34)	244 (4.24)	297 (4.02)	369 (4.34)	
37	3-pyridyl	H	228i(4.23)	246i(4.07)	310i(3.93)	365 (4.39)	

Reaction of the monobromo derivative **45** with arylhydrazine involves nucleophilic substitution, with a subsequent oxidation process analogous to the formation of oxazones (Scheme 4).

Spectral Characteristics of 6-Arylhydrazonopyridoquinazolin-4-ones.

Four tautomeric forms can be considered for the arylhydrazones **3-37** (Scheme 5). Studies on 9-arylhydrazonopyrido[1,2-*a*]pyrimidines [12,13] (corresponding to rings **C** and **D** of the present tricyclic system) invariably demonstrated the predominance of the hydrazono-imine form. Comparison of spectral data for the two series suggests that the present system also exists predominantly as this tautomer. In the uv spectra of compounds **3-37** the maximum of smallest energy is shifted to longer wavelengths by 50-100 nm as compared with the corresponding maxima at around 310 nm for the parent pyrido[2,1-*b*]quinazolines **2**. This indicates extensive conjugation between the quinazoline ring and the arylhydrazone moiety. The value of the bathochromic shift varies with the natures and positions of the substituents (λ max 365-432 nm) (Table 3).

The ^{1}H-nmr data are also in accord with the hydrazono-imine structure (Table 4). In the aliphatic region, 8-CH_2 (1.7-2.3 ppm), 7-CH_2 (2.6-2.9 ppm) and 6-CH_2 (3.7-4.3 ppm)



Scheme 6

Table 4

^{1}H Chemical Shifts for Some 6-Arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones in DMSO-d_6

Compound No.	Ar	R	9-H_2	8-H_2	7-H_2	Substituents	Ar-H	NH_E	NH_Z	*E/Z* ratio
5	4-HO-Ph	H	4.10 m	2.10 t	2.76 t		6.7-8.3 m	11.50 s	14.50 s	88:12
6	4-MeO-Ph	H	4.10 m	2.10 t	2.82 t	3.76 s	6.9-8.3 m	11.40 s	14.55 s	92:8
7	1-naphthyl	H	4.05 m	2.05 m	2.86 t		7.0-8.3 m	11.80 s	14.56 s	30:70
13	4-Me-Ph	2-Cl	4.07 m	2.00 m	2.85 t	2.50 s	7.3-8.2 m	10.80 s	14.37 s	70:30
15	2-naphthyl	H	4.10 m	2.15 t	2.85 t		7.2-8.3 m	11.15 s	14.75 s	75:25
16	4-Me-Ph	H	4.02 t	2.05 t	2.80 t	2.22 s	7.0-8.2 m	9.70 s	14.40 s	41:59
17	4-PhO-Ph	H	4.02 t	2.15 t	2.80 t		6.9-8.3 m	9.92 s	14.60 s	44:56
18	4-MeCO-Ph	H	4.03 m	2.15 t	2.85 t	2.50 s	7.3-8.3 m	10.27 s	14.74 s	29:71
19	Ph	2,3,4-$(OMe)_3$	4.00 m	2.10 t	2.82 t	3.96 s, 3.98 s 4.10 s	6.4-7.3 m	9.80 s	14.87 s	6:94
21	Ph	2-Cl	3.98 m	2.07 t	2.75 t		6.7-8.2 m	9.92 s	14.37 s	49:51
22	4-Cl-Ph	2-Cl	4.08 m	2.09 m	2.80 t		7.3-8.2 m	10.87 s	14.45 s	70:30
25	Ph	H	4.10 t	2.10 t	2.85 t		6.8-8.4 m	9.90 s	14.60 s	45:55
26	4-F-Ph	H	4.05 m	2.12 t	2.86 t		7.0-8.4 m	11.45 s	14.51 s	90:10
27	Ph	2,3-$(OMe)_2$	4.05 m	2.05 t	2.75 m	3.88 s, 3.90 s	6.6-7.6 m	9.85 s	14.40 s	34:66
28	4-Cl-Ph	H	4.02 m	2.04 t	2.74 t		7.3-8.3 m	10.00 s	14.56 s	32:68
29	4-Br-Ph	H	4.05 t	2.10 t	2.75 t		7.3-8.3 m	10.05 s	14.57 s	43:57
30	4-COOH-Ph	H	4.10 m	2.05 t	2.80 t		7.3-8.3 m	10.60 s	14.74 s	76:24
31	4-$COOC_2H_5$-Ph	H	4.02 t	2.10 t	2.83 t	1.32 t, 4.30 q	7.2-8.3 m	11.40 s	14.67 s	20:80
33	3-Cl-Ph	H	4.08 m	2.15 t	2.83 t		6.8-8.3 m	10.05 s	14.55 s	46:54
35	4-CN-Ph	H	4.05 m	2.12 t	2.78 t		7.4-8.3 m	10.35 s	14.75 s	81:19

appear as well-separated signals of two-proton intensity each. Aromatic protons give a broad multiplet at 6.4-8.3 ppm. The ^{13}C nmr data for hydrazone **25** also support the hydrazono-imine tautomeric form [2]. This form may give rise to *E/Z* isomerism associated with the C(6)=N bond. The *E:Z* ratio was found to be dependent on both the substitution and the solvent. The individual stereoisomers can be identified by the signals of the NH group in the ^{1}H nmr spectra of compounds **3-37** (Table 4). The *E* isomer, but in the latter internal steric hindrance may be offset by the internal hydrogen-bonding. Thus, in solvents less amenable to hydrogen-bonding (*e.g.* deuteriochloroform), the *Z* isomer with an internal hydrogen-bond is predominant, while in hydrogen-bonding solvents (*e.g.* DMSO-d_6) equilibrium is shifted in favour of the *E* isomer, due to hydrogen-bond formation with the solvent (Scheme 6). The *E:Z* ratio characteristic for a given solvent is established quickly, indicating the low activation energy of this process. This is in accord with earlier observations on 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [12,13].

Fischer degradation of the indole synthons to indolopyridoquinazolines will be reported later.

EXPERIMENTAL

Melting points are uncorrected and measured in capillary tubes. The uv spectra were recorded in 96% ethanol on a Unicam SP 800 instrument and ^{1}H nmr spectra in hexadeuteriodimethyl sulphoxide with tetramethylsilane as internal standard on a Bruker WP-80 FT spectrometer.

11-Oxo-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic Acid (**43**).

To a solution of 6-formyl-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**39**) [9] (2.28 g, 10 mmoles) in pyridine (15 ml) potassium permanganate (0.79 g, 5 mmoles) was added in small portions at ambient temperature. After additional stirring for 3 hours the mixture was filtered. The filtrate was diluted with water (35 ml) and the precipitated carboxylic acid **43** (0.6 g, 24%) was filtered off, washed with water, and dried, mp 175-179° dec.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 63.98; H, 5.00; N, 11.38.

Method A-1. Diazonium Coupling.

Aryldiazonium chlorides were prepared by the usual procedure [14] from aromatic amines (10 mmoles) in 20% hydrochloric acid (5 ml) at 0° with a solution of sodium nitrite (0.69 g, 10 mmoles) in water (5 ml). 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 was added dropwise at 0° a solution of the requisite 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (10 mmoles) in 50% acetic acid (10 ml). The mixture was stirred at 0° for 3 hours and allowed to stand overnight in a refrigerator. The precipitated crystalline hydrazono compound was filtered off, washed with water, dried and refluxed with ethanol (see Table 1).

Method A-2.

Diazonium coupling was carried out as described in Method A-1. The filtered hydrazono hydrochloride was dissolved in dimethylformamide (10 ml) and sodium acetate (1 g) was added. The solution was stirred at ambient temperature for 1 hour, then it was diluted with water (40 ml). The precipitated hydrazono compound was filtered off, washed with water, dried and refluxed with ethanol (see Table 1).

Method B.

To a solution of aryldiazonium chloride (prepared as described in Method A-1) a solution of 6-(dimethylaminomethylene)-6,7,8,9-tetra-

hydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**38**) [8] (2.54 g, 10 mmoles) in dimethylformamide (25 ml) was added dropwise at 0°. The reaction mixture was stirred at 0° for 3 hours and allowed to stand overnight in a refrigerator. The solution was diluted with water (50 ml) and the precipitated hydrazono derivative was filtered off, washed with water, dried and refluxed with 2-propanol (see Table 2).

Method C.

The procedure is similar to Method B, except that 6-formyl-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**39**) [9] (2.3 g, 10 mmoles) was applied instead of 6-(dimethylaminomethylene)-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one **38** (see Table 2).

Method D.

The *p*H of a solution of aryldiazonium chloride (prepared from aniline as described with Method A-1) was neutralized with 10% sodium hydroxide solution at 0°. 11-Oxo-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic acid (**43**) (2.46 g, 10 mmoles) was dissolved in 5% sodium hydroxide solution (15 ml) and it was added dropwise to the solution of an aryldiazonium chloride at 0°. The reaction mixture was stirred at 5° and allowed to stand overnight at ambient temperature. The *p*H of the reaction mixture was adjusted to 4 with acetic acid, and after 1 hour the precipitated hydrazono derivative was filtered off, washed with water, dried and refluxed with ethanol (see Table 2).

Method E.

A mixture of 6-bromo-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**45**) [11] (2.79 g, 10 mmoles) and arylhydrazine (20 mmoles) in ethanol (30 ml) was refluxed for 6 hours. The reaction mixture was evaporated to one third of its original volume. After cooling the precipitated hydrazono compound was filtered off, washed with water, dried and refluxed with ethanol (see Table 2).

Method F.

A mixture of 6,6-dibromo-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**46**) [11] (3.58 g, 10 mmoles) and arylhydrazine (40 mmoles) in ethanol (30 ml) was refluxed for 4 hours. The reaction mixture was evaporated to one third of its original volume. After cooling the precipitated crystalline product was filtered off and washed with ethanol. The crystalline product was stirred in 5% sodium acetate solution (50 ml) for 0.5 hour, then the hydrazono derivative was filtered off, washed with water, dried and refluxed with ethanol (see Table 2).

REFERENCES AND NOTES

[1] Part **44**: I. Hermecz, Á. Horváth, Z. Mészáros, C. DeVos and L. Rodriguez, *J. Med. Chem.*, in press.

[2] J. Kökösi, I. Hermecz, Gy. Szász and Z. Mészáros, *Tetrahedron Letters*, **22**, 4861 (1981).

[3a] J. H. Chu, *Sci. Rec. (China)*, **4**, 479 (1951); *Chem. Abstr.*, **46**, 11 589 (1952); [b] Ming-Tao Li and Ho-I Huang, *Yao Hsueh Hsueh Pao*, **13**, 265 (1966); *Chem. Abstr.*, **65**, 3922 (1966); [c] J. Bergman, *Alkaloids*, **21**, 49 (1983).

[4a] Ch. F. Schwender, B. R. Sunday and D. J. Herzig, *J. Med. Chem.*, **22**, 114 (1979); [b] J. W. Tilley, R. A. LaMahieu, M. Carson, R. W. Kierstead, H. Barnth and B. Yaremko, *ibid.*, **23**, 92 (1980).

[5] S. Petersen and L. Tietze, *Ann. Chem.*, **623**, 166 (1959).

[6] Kh. M. Shakhidoyatov, A. Irisbaev, L. M. Yun, E. O. Oripov and Ch. Sh. Kadyrov, *Khim. Geterotsikl. Soedin.*, 1564 (1976).

[7] T. Kametani, T. Higy, Chu Van Loc, M. Ihara, M. Koizumi and R. Fukumoto, *J. Am. Chem. Soc.*, **98**, 6186 (1976).

[8] Kh. M. Shakhidoyatov, E. O. Oripov, L. M. Yun and M. Ya. Yamankulov, *Fungitsidy*, 66 (1980); *Chem. Abstr.*, **94**, 192253 (1981).

[9] Á. Horváth, I. Hermecz, M. Pongor-Csákvári, Z. Mészáros, J. Kökösi, G. Tóth and Á. Szöllösy, *J. Heterocyclic Chem.*, **21**, 219 (1984).

[10] T. Onaka, *Tetrahedron Letters*, 4387 (1971).

[11] E. O. Oripov, Kh. M. Shakhidoyatov, Ch. Sh. Kadyrov and N. D. Abdullaev, *Khim. Geterotsikl. Soedin.*, 684 (1979); *Chem. Abstr.*, **91**, 175290 (1979).

[12] G. Tóth, B. Podányi, I. Hermecz, Á. Horváth, G. Horváth and Z. Mészáros, *J. Chem. Res.* (S), 161 (1983); (M), 1721 (1983).

[13] G. Tóth, Á. Szöllösy, A. Almássy, B. Podányi, I. Hermecz, T. Breining and Z. Mészáros, *Org. Magn. Reson.*, **21**, 687 (1983).

[14] A. I. Vogel, "Practical Organic Chemistry", Longman Group Ltd., London, 1974, pp 590-619.