Nitrogen Bridgehead Compounds. Part **81** [1]. Synthesis of 9-(Benzylidenehydrazono)-6-methyl-4-oxo-6,7,8,9-tetrahydro- and 9-(Benzylidenehydrazine)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylates

István Hermecz*, Tibor Breining, John Sessi and Benjamin Podányi

Chinoin Pharmaceutical and Chemical Works Ltd.,
H-1325 Budapest, P.O. Box 110, Hungary

Received October 16, 1990

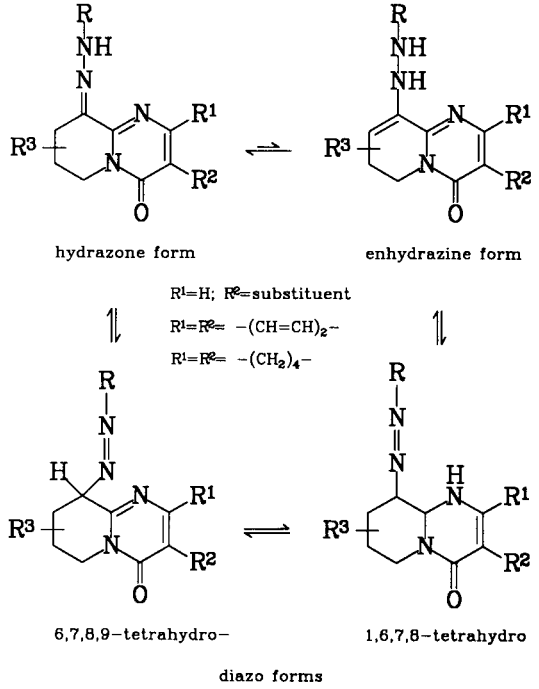
Reaction of ethyl 9-hydrazono-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and benzaldehyde and its derivatives give a tautomeric mixture of 9-arylidenehydrazono-6,7,8,9-tetrahydro- and 9-arylidenehydrazine-6,7-dihydropyrido[1,2-*a*]pyrimidine derivatives. In the same case the enhydrazine and hydrazone tautomers were separated. The structure of the products were characterised by uv, ir, ^{1}H and ^{13}C nmr. The equilibrium of the tautomers was affected by the substituent of the phenyl ring. A fair linear correlation exists between the logarithms of the equilibrium constants and Hammett σ_m and σ^- constants of the substituents present on the phenyl ring.

J. Heterocyclic Chem., **28**, 781 (1991).

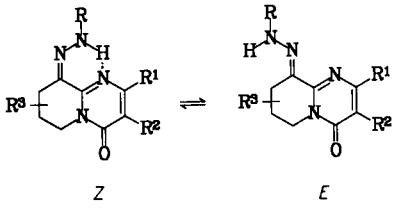
Introduction.

At the investigations of the structures of 9-hydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-4-ones [2-4] and their benzolog [5,6] or the latters' tetrahydro derivatives [7], (6-hydrazono-6,7,8,9-tetrahydro-or 1,2,3,4,-6,7,8,9-octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones) four possible tautomers were taken into considerations (see Scheme 1). Detailed nmr investigations revealed that hydrazone forms were predominate, which exhibited a solvent-dependent *E-Z* isomerism (Scheme 2) [2,3,5,7]. The presence of the sterically crowded *Z* isomer, in the equilibrium mixture, was the consequence of the internal hydrogen bond developed between *N*-1 and (*N*-2')H atoms [2]. The existence of the *Z* isomer could not be detected for *N,N*-disubstituted hydrazones. The tautomerism and isomerisation of 9-hydrazono-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones were also studied by uv methods [8,9]. For the latter study the fixed forms of 9-diazo-6,7,8,9- and 1,6,7,8-tetrahydro tautomers were also prepared and investigated [4,8].

Scheme 1



Scheme 2



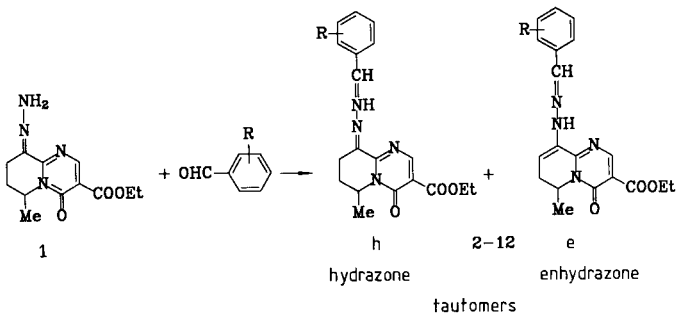
The Fischer indolization of 6-hydrazonopyridoquinazolinones gave a facile synthetic method for the preparation of rutaecarpine alkaloid (7,8-dihydro-5*H*,13*H*-indolo[2',-3':3,4]pyrido[2,1-*b*]quinazolin-5-one) [6] and its derivatives [7,10]. Earlier it was unambiguously justified that the Fischer indolization of arylhydrazone derivatives occurred from the enhydrazine tautomeric form [11,12].

In this paper we report on the synthesis and the investigations of such 9-hydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates which exhibit a hydrazone-enhydrazine tautomerism.

Chemistry.

In the reaction of ethyl 9-hydrazone-6-methyl-4-oxo-6,7,-8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1**) [2] with benzaldehyde in dimethyl sulphoxide at room temperature for 6 days the formations of two products was indicated by tlc. Two products **2e** and **2h** were separated by the use of preparative tlc (see Experimental Section). The product with a higher Rf value proved to be the

enhydrazone tautomer **2e**, while the other the hydrazone **2h** (see below).



9-Hydrazonopyridopyrimidine (**1**) was reacted further aromatic aldehydes in boiling ethanol (Method A) or in chloroform in the presence of one drop of ethanolic hydrogen chloride at ambient temperature (Method B). When 4-nitrobenzaldehyde was reacted with compound **1** according to Method B the reaction mixture contained mainly hydrazone tautomer **10h**, but when the row product was boiled in acetonitrile the ratio of the two tautomers was reversed. The reaction of 3-nitrobenzaldehide in ethanol afforded almost pure hydrazone form **9h**, but the reaction in boiling acetonitrile (Method C) resulted in the formation of an isomeric mixture with the predominance of enhydrazine tautomer **9e** (see Table 1).

Table 2

UV Data on Compounds **1-3,7,9** and **10** in Ethanol

Compound	R	λ, nm (ε)		
1		358 (22840),	295 (6250),	274i (3850)
2h	H	343 (19590),	280 (13270),	231i (91209)
3h	4-NMe_2	456 (25420), 264 (9350)	354 (10550),	307 (11030),
9h	3-NO_2	340 (16870),	266 (22220)	
10h	4-NO_2	346 (19300),	306 (17710)	
2e	H	385i (4070), 227 (13300)	330 (27440),	271 (11830),
7e	4-Cl [a]	390i, 232	335,	272,
9e	3-NO_2 [a]	386i,	333,	260
10e	4-NO_2	402 (21440), 262 (17950),	380 (21500), 235i (14100)	340i (18630),

h Hydrazone tautomer, e Enhydrazine tautomer. [a] In saturated solution.

Table 1

Physical and Analytical Data on Compounds **3-12**

Compounds	R	Method	Yield %	Mp °C	Enhydrazine content [a] %	Formula	Analysis Calcd./Found % C	H	N	Halogen
3h	4-NMe_2	A-1	66.6	163 (AcOEt)	5	$C_{21}H_{25}N_5O_3$	63.78 63.74	6.37 6.28	17.71 17.58	
4e	4-Me	A-1	21.7	172-173 (Et_2O) [b]	70	$C_{20}H_{22}N_4O_3$	65.56 65.80	6.05 6.11	15.29 15.08	
		B	72.4	168-170 (Et_2O) [b]	70					
5	3-Me	B	50.7	140-142 (Et_2O) [b]	59	$C_{20}H_{22}N_4O_3$	65.56 65.74	6.05 5.89	15.29 15.30	
6	4-Br	B	61.3	202-204 (MeCN) [b]	32	$C_{19}H_{19}BrN_4O_3$	52.91 53.09	4.44 4.38	12.99 12.91	18.53 18.72
7e	4-Cl	B	71.8	198-200 (MeOH)	80	$C_{19}H_{19}ClN_4O_3$	58.99 58.83	4.95 5.04	14.48 14.40	9.17 9.29
8e	3-Cl	B	82.9	164-166 (MeCN)	83	$C_{19}H_{19}ClN_4O_3$	58.99 59.11	4.95 4.88	14.48 14.59	9.17 9.20
9h	3-NO_2	A-2	86.5	132 (EtOH)	5	$C_{19}H_{19}N_5O_5$	57.43 57.49	4.82 4.90	17.62 17.48	
9e	3-NO_2	C	73.2	214-216 (MeOH) [b]	84	$C_{19}H_{19}N_5O_5$	57.43 57.71	4.82 4.91	17.62 17.61	
10h	4-NO_2	A-1	98.2	168-170 (EtOH)	5	$C_{19}H_{19}N_5O_5$	57.43 57.61	4.82 4.58	17.62 17.77	
10e	4-NO_2	B	93.2	145-147 (MeCN) [b]	86	$C_{19}H_{19}N_5O_5$	57.43 57.62	4.82 4.95	17.62 17.48	
11h	3-OH	B	72.2	202-204 (MeCN) [b]	10	$C_{19}H_{20}N_4O_4$	61.94 61.76	5.47 5.55	15.21 15.30	
12h	4-OH	B	79.4	125-127 (MeOH-H_2O = 3:1)	5	$C_{19}H_{20}N_4O_4$	61.94 62.14	5.47 5.46	15.21 15.14	

h Hydrazone tautomer, e Enhydrazine tautomer. [a] The content of enhydrazine tautomer was estimated on the basis of the intensity of H-8 of enhydrazine from the ^1H nmr. [b] Boiled in the solvent given.

Table 3

^{1}H NMR Chemical Shifts and Multiplicities for Hydrazone and Enhydrazine Tautomers of Compound **2** in deuteriochloroform [δ TMS = 0.00 ppm]

Compound	2-H	6-H_{eq}	7-H_{eq}	7-H_{ax}	8-H or 8-H_2	-CH=	6-Me	OCH_2—CH_3		NH	Ph
2h	8.78 s	5.10-5.50 m	1.80 -	2.28 m	2.60-3.32 m	8.50 s	1.41 d	4.35 q	1.41 t		7.30-7.95 m
2e	8.63 s	5.10-5.50 m	2.46 ddd [a]	2.94 ddd [a]	6.18 ddd [a]	8.55 s	1.38 d	4.42 q	1.42 t	8.87 s	7.25-7.80 m

h Hydrazone tautomer, **e** Enhydrazine tautomer. [a] $^2J_{7c,7a} \approx 18.3$ Hz, $^3J_{6e,7e} \approx 1.6$ Hz. [b] $^3J_{6e,7a} \approx 6.9$ Hz. [c] $^3J_{7e,8} \approx 7.1$ Hz, $^3J_{7a,8} \approx 3.1$ Hz, $^4J_{6e,8} \approx 1.2$ Hz.

Table 4

Characteristics ^{1}H NMR Chemical Shifts for Compounds **1** and **3-12** in deuteriochloroform [δ TMS = 0.00 ppm]

Compound	R	Hydrazone Tautomers		Enhydrazine		
		2-H	-CH= [a]	2-H	-CH= [a]	8-H
1 [b]		8.72 s [c]				
3	4-NMe_2	8.80 s	8.65	8.70 s	8.78	5.80 m
4	4-Me	8.78 s	8.52	8.60 s	8.45	6.15 m
5	3-Me	8.82 s	8.52	8.62 s	8.67	6.18 m
6	4-Br	8.82 s	8.50	8.62 s	8.70	6.18 m
7	4-Cl	8.88 s	8.58	8.60 s [d]	8.60 [d]	6.20 m
8	3-Cl	8.82 s	8.48	8.62 s [e]	8.62 [e]	6.20 m
9	3-NO_2	8.80 s	8.55	8.66 s	8.85	6.30 m
10	4-NO_2	8.79 s	8.50	8.62 s	8.90	6.26 m
11	3-OH	8.80 s	8.45	8.65 s		6.18 m
12	4-OH	8.82 s	8.53			

[a] Broad singlet. [b] 85:15 Mixture of *E* and *Z* isomers. [c] Chemical shifts of *E* isomer, $\delta_{2H(Z)} = 8.68$ ppm. [d] Overlaping signs. [e] Overlaping signs.

Table 5

^{13}C NMR Chemical Shifts of Compounds **2, 3** and **10**

[δ TMS = 0.00 ppm]

	Compound			
	2h [a]	**2e** [a]	**3h** [b]	**10h** [a]
C-2	157.6		157.9	157.5
C-3	116.4	115.9	115.6	116.9
C-4	157.4		157.6	157.4
C-6	46.8	45.1	46.7	46.9
C-7	25.2	27.3	25.3	25.2
C-8	21.7	103.7	21.5	21.9
C-9	155.0		155.6 [c]	154.9
C-9a	157.4	135.3	156.4 [c]	157.2
3-CO	163.7		164.0	163.8
=CH-	160.1	161.8	164.1	156.2
6-CH_3	17.5		17.5	17.7
OCH_2	61.2		61.1	61.5
CH_2CH_3	14.3		14.3	14.3
C-1'	133.8	135.3	121.4	139.4
C-2',6'	129.0		131.4	129.3
C-3',5'	129.0		111.8	124.3
C-4'	132.1		153.4	149.8
NMe_2			40.0	

[a] In deuteriochloroform. [b] In DMSO-d_6. [c] Tentative assignment.

Spectroscopic Studies.

Some characteristics uv, ^{1}H and ^{13}C nmr data are tabulated in Tables 2-5.

In the ir spectra (potassium bromide) the presence of the enhydrazine tautomer is indicated by the sharp absorption band of NH group at around 3300 cm^{-1}.

In the ^{1}H mmr spectra (deuteriochloroform) the chemical shifts of H-2 of hydrazone tautomers appeared at lower field than that of H-2 of enhydrazine tautomers (hydrazone $\delta_{H-2} \approx$ 8.78-8.85 ppm, enhydrazine $\delta_{H-2} \approx$ 8.60-8.70 ppm).

The enhydrazine tautomer can be distinquised in the ^{1}H nmr spectra by the chemical shift of H-8 appeared around 6.00 ppm.

Because of the lack of stabilization factors (*e.g.* the formation a hydrogen bond) the C=N double bonds in both hydrazone and enhydrazine tautomers adopt most likely the sterically less crowded *E* conformations.

The interconversion between the hydrazone and enhydrazine tautomers could be catalyzed by acid. When solutions of arylhydrazones **2-10** in deuteriochloroform ($\sim 5.5 \times 10^{-5}$ *M*) were left to stand for 2 days in the presence of trifluoroacetic acid equilibrium mixtures were obtained. The amount of the enhydrazine tautomers were determined by ^{1}H nmr spectroscopy, comparing the intensity of H-8 of enhydrazine with that of H-6 of pyridopyrimidine skeleton. The ratio of the two tautomeric forms was affected by the substituent of the phenyl ring. The presence of an electron withdrawing substituent shifts the equilibrium to the enhydrazine tautomer by stabilizing

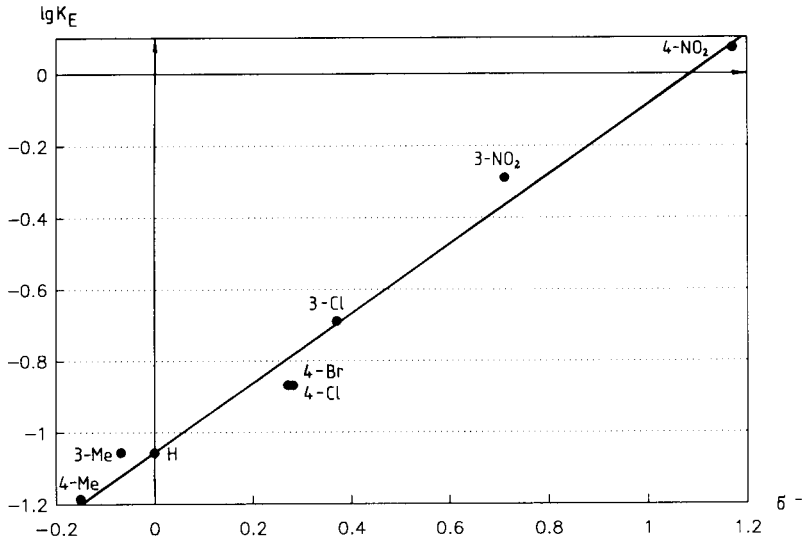
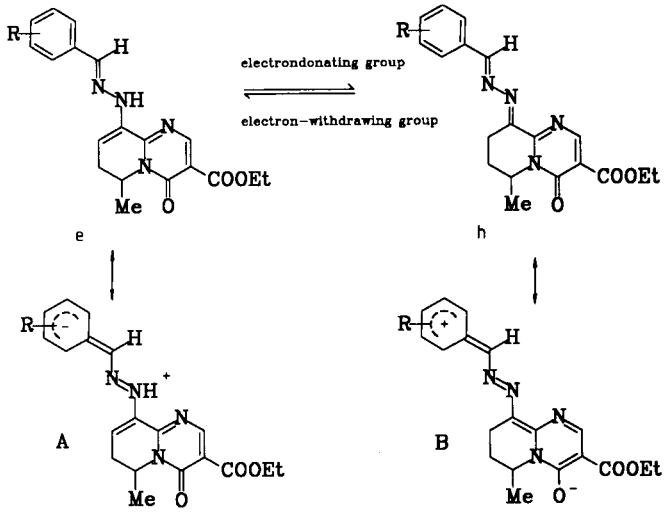


Figure 1. Relationship between lgk^E and substituent (R) constants, σ^- and σ_m; $lgK_E = (0.983 \pm 0.054) - 1.058 \pm 0.063$; $r^2 = 0.982$.

the ionic canonical form **A** (see Scheme 3), while the electrondonating groups stabilize the mesomeric form **B** of the hydrazono tautomer (see Scheme 3).

Scheme 3



A fair linear correlation was obtained when the logarithms of the equilibrium constants were plotted against σ^- constant of the para substituent of the phenyl ring [13] and σ_m constant of the *meta* substituent [14] (see Figure 1 and Table 6).

Table 6

Equilibrium Contents of 9-Arylidenehydrazonopyridopyrimidin-3-carboxylates **2** and **4-10**

Compound	R	Enhydrazine content [a]	K_E [b]	lgK_E	σ^- [c]	σ_m [d]
10	4-NO_2	54	1.17	0.07	1.17	
9	3-NO_2	34	0.52	-0.29		0.71
8	3-Cl	17	0.20	-0.69		0.37
6	4-Br	12	0.14	-0.87	0.28	
7	4-Cl	12	0.14	-0.87	0.27	
2	H	8	0.09	-1.06	0.00	
5	3-Me	8	0.09	-1.06		-0.07
4	4-Me	6	0.06	-1.19	-0.15	

[a] The amount of enhydrazine tautomer in the equilibrium after 2 days in a solution of deuteriochloroform and trifluoracetic acid. [b] K_E = e% / h%. [c] Ref 13. [d] Ref 14.

EXPERIMENTAL

Melting points were uncorrected. Yields were not optimized. The uv spectra were recorded on a Unicam SP-800 spectrophotometer. The ir spectra were recorded for KBr pellets with a Zeiss UR-20 spectrophotometer. The ^1H and ^{13}C nmr spectra were measured on a Bruker WP-80 spectrometer at 80 MHz and 20.1 MHz, respectively. Chemical shifts are given on δ scale, and TMS was used as internal standard.

Reaction of Ethyl 9-Hydrazono-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and Benzaldehyde.

A mixture of ethyl 9-hydrazonopyrido[1,2-*a*]pyrimidine-3-carboxylate (**1**) [2] (2.0 g, 7.57 mmoles) and benzaldehide (1.12 g, 11.88 mmoles) in dimethyl sulphoxide (12 ml) was left to stand at ambient temperature for 6 days. The reaction mixture was diluted with water (20 ml) and it was extracted with benzene (3 x 30 ml). The combined and dried (sodium sulfate) organic phase was evaporated to dryness *in vacuo*. The oily residue was crystallized

by the treatment of diethyl ether (20 ml). The crystals were filtered off, and washed with diethyl ether to give 2.0 g (75%) of a mixture of **2h** and **2e**, mp 140°.

Compounds **2h** and **2e** were separated on a preparative Kieselgel 60 $PF_{254+366}$ plate (Merck). Developing system: benzene: methanol = 7:1. Eluent system: methanol: methylene chloride = 1:10.

Ethyl 9-(Benzylidenehydrazono)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**2h**).

Compound **2h** with lower Rf value had mp 142-144°, 0.12 g, (methanol); ir (potassium bromide): ν max 1736, 1708, 1680 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.77; H, 5.72; N, 15.89. Found: C, 64.53; H, 5.53; N, 15.82.

Ethyl 9-(benzylidenehydrazino-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**2e**).

Compound **2e** with higher Rf value had mp 133-134°, 0.75 g, (methanol); ir (potassium bromide): ν max 3330, 1738, 1706, 1680 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.77; H, 5.72; N, 15.89. Found: C, 64.59; H, 5.68; N, 15.96.

Method A-1.

A solution of 9-hydrazonopyridopyrimidine **1** [2] (0.5 g, 1.89 mmoles) and the appropriate aldehyde (2.83 mmoles) in ethanol (3 ml) was refluxed for 5 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was crystallized by the treatment of diethyl ether.

Method A-2.

A solution of 9-hydrazonopyridopyrimidine **1** [2] (0.5 g, 1.89 mmoles) and the appropriate aldehyde (2.83 mmoles) in ethanol (10 ml) was boiled for 3 hours. The reaction mixture was cooled to 0° and the crystalline product was filtered off. The mother liquour was evaporated to dryness *in vacuo*. The residue was crystallized by the treatment of ethanol. The combined crystals were recrystallized.

Method B

A solution of 9-hydrazonopyridopyrimidine **1** [2] (0.5 g, 1.89 mmoles) and the appropriate aldehyde (2.83 mmoles) in chloroform (5 ml) and one drop of ethanol containing 20% hydrogen chloride was left to stand at room temperature for 24 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was crystallized by the treatment of diethyl ether.

Method C.

A solution of 9-hydrazonopyridopyrimidine (**1**) [2] (0.5 g, 1.89 mmoles) and the appropriate aldehyde (2.83 mmoles) in acetonitrile (10 ml) was boiled for 6 hours. The reaction mixture was cooled to 0° and the crystalline product was filtered off.

REFERENCES AND NOTES

[1] I. Hermecz, T. Breining, K. Simon, B. Podányi and J. Sessi, to be published.

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

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

[4] I. Hermecz, T. Breining, Z. Mészáros, A. Horváth, L. Vasvári-Debreczy, F. Dessy, C. DeVos, and L. Rodriguez, *J. Med. Chem.*, **25**, 1140 (1982).

[5] J. Kökösi, I. Hermecz, B. Podányi, Gy. Szász, and Z. Mészáros, *J. Heterocyclic Chem.*, **21**, 1301 (1984).

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

[7] I. Hermecz, J. Kökösi, A. Horváth, B. Podányi, L. Vasvári-Debreczy, Gy. Szász, and Z. Mészáros, *J. Heterocyclic Chem.*, **24**, 1045 (1987).

[8] G. Horváth, T. Breining, I. Hermecz, A. Horváth, M. Pongor-Csákvári, B. Podányi, A. I. Kiss, and A. Martin, *Acta Chim. Hung.*, **119**, 305 (1985).

[9] A. Martin, A. I. Kiss, G. Horváth, and I. Hermecz, *Acta Chim. Hung.*, **119**, 321 (1985).

[10] J. Kökösi, I. Hermecz, B. Podányi, Gy. Szász, and Z. Mészáros, *J. Heterocyclic Chem.*, **22**, 1373 (1985).

[11] B. Robinson, The Fischer Indole Synthesis, John Wiley and Sons, New York, 1982.

[12] B. Robinson and R. Robinson, *J. Chem. Soc.*, **113**, 639 (1918).

[13] A. Fischer, G. J. Leary, R. D. Topson, and J. Vaughan, *J. Chem. Soc. B*, 846 (1967).

[14] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).