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SYNTHESIS, OXIDATION AND DEHYDROGENATION OF CYCLIC *N,O*- AND *N,S*-ACETALS. PART 1. TRANSFORMATION OF *N,S*-ACETALS: 3-ACYL-1,3,4-THIADIAZOLINES

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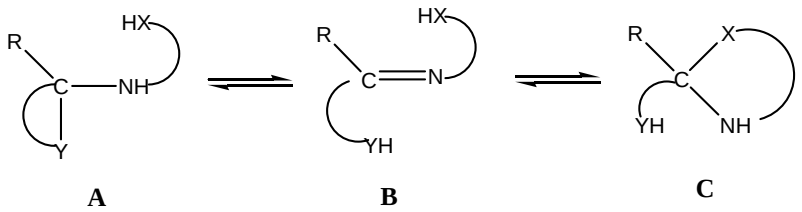
Abstract – Aldehyde and ketone thiosemicarbazones are synthesized and cyclized into 3-acyl-1,3,4-thiadiazolines under acylating conditions. Reactions of the 2-monosubstituted heterocycles with oxidizing and dehydrogenating agents ($KMnO_4$ or for the first time with CAN, DDQ, IBDA) lead to the formation of thiadiazoles. CAN oxidation of 2,2-disubstituted 3-acyl-1,3,4-thiadiazolines regenerates the parent ketones efficiently.

INTRODUCTION

The formation of cyclic *N,O*- and *N,S*-acetals can be formally described by addition of an OH or SH group, located in the carbonyl or amino portion of the open-chain molecule, to the C=N bond (Scheme 1). The structure of the cyclic compound formed in this way, and the state of the equilibrium are determined by the electronic, steric and thermodynamic properties of the molecules and the nucleophilicity of the heteroatoms X and Y, respectively.

The ring-chain tautomerism[1] is a very important phenomenon from chemical and biological point of view [glycosylamines, sugar-amino acid condensates, etc.; e.g. to D-galactose thiosemicarbazone an open-chain hydrazone (**B**, Scheme 1) and a pyranose (**A**) structure,[2] respectively, to the D-glucose derivative a glucosylamine structure (**A**),[3] to the ligand of a 1:1 complex of D-glucose thiosemicarbazone with $CuCl_2$, however, a 2-amino-5-(D-*gluco*-pentahydroxy)pentyl-1,3,4-thiadiazol-5-ine structure (**C**)[4] have been attributed]. The cyclic or open-chain isomers can be stabilized chemically, e.g. by acetylation,[5] whereby modifying solubility, biological absorption (membrane and barrier permeability) and activity. Chemical as well as microbial or enzymic deacetylation[6a-e] (phase 1 metabolism) can lead to (re)cyclization or to regeneration of the original isomerizable compound and the parent acid hydrazide[6f–h] respectively.



A **B** **C**

Scheme 1

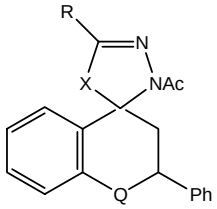
Dehydrogenation of aldehyde cyclic *N*,*O*- or *N*,*S*-acetals, the latter is a spontaneous process occasionally, seems to be a versatile and promising alternative route for the synthesis of various 2-substituted 1,3-azoles and 1,3-azines, respectively. – It should also be noted, however, that some dehydrogenation products, e.g. 1,3,4-oxadiazoles[7] and 1,3,4-thiadiazoles[8] undergo recyclization with intra- or intermolecular nucleophiles.

The chemistry of 1,3,4-thiadiazol(in)es[1b,c,e,g,9a,10] as biologically active[9b,c,11,12] and/or complex-forming[11p,13] substances is well documented and has been enormously extended if only in view of late ~15 years, as well. 2,5-Disubstituted 1,3,4-thiadiazoles have been synthesized by cyclization of *N*,*N*′-di(thio)acylhydrazines,[14] by condensing thioacid hydrazides with trichloromethanes,[15] carboxylic acids,[16] iminoesters,[17] or (iso)nitriles[16d,18] (eventually, however, under vigorous conditions), moreover by treating aldehyde thioacylhydrazones (including thiosemicarbazones) with $FeCl_3$,[13a,19a–w] $K_3[Fe(CN)_6]$,[19g,20] MnO_2,[21] Br_2/AcOH,[22] or DDQ.[23] On the other hand, DDQ cyclizes 4-substituted thiosemicarbazides into 5-substituted imino-Δ^3-2,1,3,4-oxathiadiazolines and -2,2-dioxo-Δ^3-1,2,3,4-dithiadiazolines,[24] *N*-benzylidene-2-hydroxyanilines into 2-substituted phenylbenzoxazoles,[25] and cleaves tosylhydrazones or oximes to the parent carbonyl compounds.[26] In addition, 2,5-disubstituted 1,3,4-thiadiazoles have been prepared, in an uncommon reaction, by treating aldehyde thiosemicarbazones with NaOAc/NaBr/AcOH,[27] as well as by transforming 1,3,4-oxadiazoles with thiourea[7d] and 1,2,4,5-tetrazines with sulfur,[28] respectively. Of the various 1,3,4-thiadiazole syntheses, for this once, mostly the dehydrocyclization reactions will be considered.

Thioacylhydrazines react with carbonyl compounds to give immediately the corresponding 1,3,4-thiadiazolines[11d,29] or sometimes their prototrops forms.[11d,29g] Thiosemicarbazones undergo similar cyclization, mainly in acid medium to form an equilibrium mixture of the open-chain and prototrop cyclic entities.[11b,e,19m,30] Some aldehyde thiobenzoylhydrazones exist as Δ^2-thiadiazolines also in solution and are spontaneously dehydrogenated by prolonged heating,[29c,31] or by oxygen at room temperature,[19c,x,29d] to afford 1,3,4-thiadiazoles. With respect to the ring-chain tautomerism and the prototropy mentioned above, stabilization of the cyclic form is suitable. Under acylating conditions thioacylhydrazones, including thiosemicarbazones, undergo transformation to 5-substituted 3-acyl-1,3,4-thiadiazolines[1i,14c,32] instead of

N,*S*-diacyl-thiosemicarbazones as have been suggested previously.[13a,19 l,33] Dehydrogenation of the 3-acylthiadiazolines by treating with H_2O_2,[19 l,33c,d] $FeCl_3$,[32a,d] or $KMnO_4$[21,32d] has been reported to afford 1,3,4-thiadiazoles.

As an extension of our previous works with spiro[tetrahydroquinoline-4,2′-[1,3,4]thiadiazoline] (**11a**)[34] and spiro[flavan-4,2′-[1,3,4]oxa(thia)diazolines] (**11b,c**)[32h] the analogous thioflavan spirocompounds (**11d,e**) have been synthesized[35] and, for obtaining the corresponding thioflaven analogs subjected to transformation with CAN capable[36] of dehydrogenating thioflavanone to thioflavone. When treating **11e** with CAN, however, thioflavone formed with degradation of the thiadiazoline moiety.[35] Owing to these difficulties, the oxidation and dehydrogenation reactions of 1-thiobenzopyran[37] and diazoline rings, respectively, have been separately investigated. In this paper the works aimed at the transformation of 1,3,4-thiadiazolines by oxidizing and dehydrogenating agents are presented.



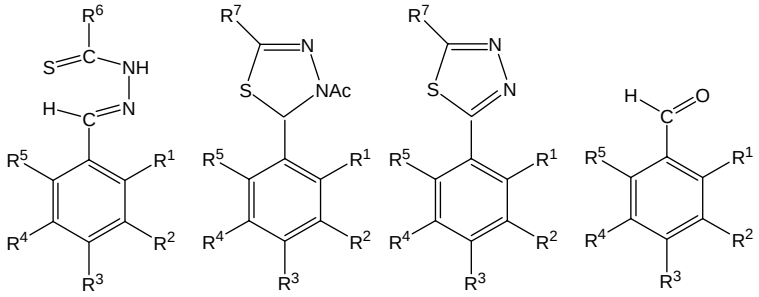
11

	Q	X	R
11a	NAc	S	NHAc
11b	O	S	NHAc
11c	O	O	Me
11d	S	O	R^1
11e	S	S	NR^2R^3

R^1= Me, Ph; R^2= H, Ph; R^3= Ac

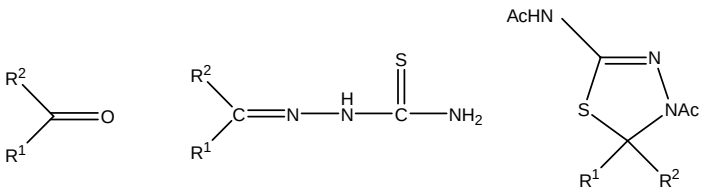
RESULTS AND DISCUSSION

The electronic structure and chemical reactivity of a C=N bond is influenced by the electronic properties of the substituents (see e.g. ref. 38). Thus, thiosemicarbazones of various benzaldehydes diversely substituted as regards the position, number, bulk, electronic properties, and reactivity of the substituents (**1**, see also Table 1) were prepared and, under acetylating conditions (Ac_2O, Ac_2O/pyridine, $Ac_2O/ZnCl_2$), cyclized into 3-acetyl[1,3,4]thiadiazolines (**2**, Table 2). These compounds are substrates for subsequent reactions with various types of oxidants and dehydrogenating agents of diverse mechanisms of action (see Table 3). For explorating such cyclization reactions, some additional aldehyde and ketone thiosemicarbazones (**6**) were prepared and converted into thiadiazolines (**7**) (see Tables 6,7). The structure of the products was supported by ^{1}H- and ^{13}C NMR spectral data (see Tables 4,5,8).



1 **2** **3** **4**

	R^1	R^2	R^3	R^4	R^5	R^6	R^7
a	H	H	Cl	H	H	NH_2	NHAc
b	H	H	NO_2	H	H	NH_2	NHAc
c	Cl	H	H	H	Cl	NH_2	NHAc
d	Cl	H	H	H	Cl	NHPh	NAcPh
e	Cl	NO_2	H	H	Cl	NH_2	NHAc
f	H	Cl	Cl	H	H	NH_2	NHAc
g	H	OMe	OMe	OMe	H	NH_2	NHAc
h	OMe	H	OMe	H	OMe	NH_2	NHAc



5 **6** **7**

	R^1	R^2
a	4-ClC_6H_4	Me
b	4-BrC_6H_4	Me
c	2-pyridyl	Me
d	2,4-$(HO)_2C_6H_3$	Me
e	2,4-$(AcO)_2C_6H_3$	Me
f	Indol-3-yl	H
g	1-(Ac)indol-3-yl	H

The acetylating agents used (and others e.g. AcCl/Me_2NPh, Ac_2O/Et_3N) are reported, however, also to transform[2,32h,39,40] thiosemicarbazones into acylhydrazones and diacylhydrazones or *N*-triacetyl-enehydrazines. On this subject, especially the $Ac_2O/ZnCl_2$ couple is capable of producing transformations of various types. This agent is known to acetylate thiosemicarbazones at position 4,[39] and to cyclize (thio)acylhydrazones into 3-acetyl[1,3,4]oxa(thia)diazolines.[41]

Table 1. Preparation and properties of thiosemicarbazones (**1**)

Product	Reaction components (mmol)	Solvent (mL)	Reaction temp. [°C][a] (time [h])	Workup[b]	Yield [%] crude[c] (pure)[c]
1a	**4a** (40) TSC (42)	AcOH (30)	100 (3)	A	80
1b	**4b** (20) TSC (30)	AcOH (20)	100 (2)	A	90
1c	**4c** (10) TSC (10.5)	MeOH[f] (20)	bp (1.5)	A	99.5
1d[h]	**4d** (10) PTSC (10)	EtOAc (8)	bp (1.5)	A	95.5
1e	**4e**[i] (20) TSC (23)	AcOH (20)	100 (2)	A[j]	96.4
1f	**4f** (60) TSC (63)	MeOH[l] (75)	bp (3.5)	A	85
1g	**4g** (20) TSC (21)	MeOH[o] (35)	bp (6)	A	97
1h	**4h** (20) TSC (21)	MeOH[o] (40)	bp (2.5)	A	96 (94)

Table 1. Preparation and properties of thiosemicarbazones (**1**) (continued)

Product	Mp [°C] (solvent)	Lit. mp [°C] (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
1a	215[d]	220[e] (aq.EtOH)	$C_8H_8N_3ClS$ (213.7)			
1b	243[d]	255[e] (95% EtOH)	$C_8H_8N_4O_2S$ (224.2)			
1c	237[d]	236–237[g] (EtOH)	$C_8H_7N_3Cl_2S$ (248.1)			
1d[h]	208–209[d]		$C_{14}H_{11}N_3Cl_2S$ (324.2)	52.07 (51.86)	3.49 (3.42)	13.08[h] (12.96)
1e	229–230[d] 234–235 (MeOH)		$C_8H_6N_4O_2Cl_2S$ (293.1)	33.28 (32.78)	2.51 (2.06)	18.93[k] (19.11)
1f	214–215[d,m] 216 (MeOH)	194–195 (EtOH)[n]	$C_8H_7N_3Cl_2S$ (248.1)	38.94 (38.72)	2.86 (2.84)	16.87 (16.94)
1g	206–207[d] 209–210 (EtOH)	216–217[p] (DMF/EtOH)	$C_{11}H_{15}N_3O_3S$ (269.3)	49.33 (49.05)	5.60 (5.61)	15.70[q] (15.60)
1h	160–162 (DMF/H_2O)		$C_{11}H_{15}N_3O_3S$ (269.3)	49.22 (49.05)	5.71 (5.61)	15.68[r] (15.60)

TSC = thiosemicarbazide, PTSC = 4-phenyl-3-thiosemicarbazide. [a] Bath if not bp. [b] For general operations of processing the reaction mixtures see EXPERIMENTAL. [c] Without workup of the mother liquors. [d] Crude product. [e] Corrected, ref. 53. [f] Containing 0.5 mL AcOH. [g] Ref. 54. [h] Cl 21.98 (21.87), S 10.05 (9.89). The same product was obtained in 71% yield when treating 2,6-dichlorobenzaldehyde hydrazone (1mmol) with PhNCS (1.1 mmol) in boiling EtOAc (2 mL) for 1.5 h; mp 206–208 °C (from pyridine with addition of water). [i] Ref. 55. [j] Previously water (10 mL) was added. [k] Cl 24.04 (24.19), S 11.01 (10.94). [l] Containing 3 mL AcOH. [m] TLC [PhH/EtOAc (1:2)] homogeneous. [n] Ref. 19b. [o] Containing 1 mL AcOH. [p] Ref. 56; ref. 57 : mp 215–216 °C. [q] S 11.87 (11.91). [r] S 11.66 (11.91).

By heating above the melting point, 5-acetamido-3-acetyl-2-(4-nitrophenyl)-1,3,4-thiadiazoline (**2b**) was dehydrogenated to thiadiazole (**3b**) in 88% yield (see EXPERIMENTAL). Hitherto thermolysis of 2,5-disubstituted 3-nitroso-1,3,4-thiadiazolines[19m] and of a spiro-Δ^3-1,3,4-thiadiazoline with C—O bond cleavage to give a 2-substituted 1,3,4-thiadiazole have been reported.[42] Also dehydrogenation of ketone cyclic *N*,*S*-acetals with concomitant reductive C—C bond cleavage resulting in the formation of benzothiazole[43] and 1,3,4-thiadiazole[19d,44] derivatives, respectively, has been observed perviously. Moreover, when treating a carbohydrate aldehyde thiosemicarbazone with Ac_2O/pyridine, in addition to the expected formation of the corresponding 2-substituted 5-acetamido-3-acetyl-1,3,4-thiadiazoline the

Table 2. Preparation and properties of 1,3,4-thiadiazolines (**2**)

Product	Substrate (mmol)	Agents (mmol)	Reaction temp. [°C][a] (time [h])	Workup[b]	Yield[%] crude (pure)[c]
2a	**1a** (20)	Ac_2O (233)	bp (2)	C, D, A	90[e]
2b	**1b** (9)	Ac_2O (53)	bp (0.5)	B	98[f]
2c	**1c** (40)	Ac_2O (530)	bp (1)	A	95
	1c (4)	Ac_2O (106) $ZnCl_2$ (11)	55 (5)	A	95
2d	**1d** (6)	Ac_2O (106) py[l] (124)	23 (24)	B	97 (80)
2e	**1e** (63)	Ac_2O (1060)	bp (0.75)	A	96 (88)
2f	**1f** (16)	Ac_2O (212)	bp (2)	A	85 (70)
2g	**1g** (22)	Ac_2O (159)	bp (0.5)	C, E	99 (86)
2h	**1h** (1.9)	Ac_2O (27)	bp (2)	B	69 (27)

Table 2. Preparation and properties of 1,3,4-thiadiazolines (**2**) (continued)

Product	Mp [°C] (solvent)	Lit. mp [°C] (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
2a	247[d] (EtOH)	229–233[e] (EtOH)	$C_{12}H_{12}N_3O_2ClS$ (297.8)			
2b	227[d] 230 (EtOH)	210–211[f] (EtOH)	$C_{12}H_{12}N_4O_4S$ (308.3)	46.89 (46.74)	3.92 (3.92)	18.16[g] (18.17)
2c	203[d] 236–237 ($DMSO/H_2O$)[h] 235–236[d] 203–204 ($DMSO/H_2O$)[h]		$C_{12}H_{11}N_3O_2Cl_2S$ (332.2)	43.88 (43.38)	3.54 (3.34)	12.34[i] (12.65)
2d	183 (EtOAc/heptane)		$C_{18}H_{15}N_3O_2Cl_2S$ (408.3)	53.12 (52.95)	3.70 (3.70)	10.34[j] (10.29)
2e	266–267[d] 271–272 (Ac_2O)		$C_{12}H_{10}N_4O_4Cl_2S$ (377.2)	38.42 (38.21)	2.70 (2.67)	14.90[k] (14.85)
2f	202–204[d] 203 ($EtOH^l$/heptane)		$C_{12}H_{11}N_3O_2Cl_2S$ (332.2)	43.56 (43.38)	3.40 (3.34)	12.68[m] (12.65)
2g	164[d,n] 166–167 (MEK)[o]		$C_{15}H_{19}N_3O_5S$ (353.4)	51.03 (50.98)	5.63 (5.42)	12.18[p] (11.89)
2h	218–219 ($CHCl_3$/EtOAc)		$C_{15}H_{19}N_3O_5S$ (353.4)	51.15 (50.98)	5.50 (5.42)	12.07[q] (11.89)

[a] Bath if not bp. [b] For general operation of processing the reaction mixtures see EXPERIMENTAL. [c] Without workup of the mother liquors. [d] Crude product. [e] Ref. 32a, d, yield 68%. [f] Ref. 32a, d , yield 57%. [g] S 10.67 (10.40). [h] From hot DMSO solution with addition of water. When recrystallized from $AcOH/H_2O$ or DMF/H_2O **2c** contains some AcOH and DMF, recpectively, as a solvate. [i] Cl 21.05 (21.35), S 9.73 (9.65); before the analysis **2c** was kept at 100 °C/0.1 Torr over P_4O_{10}. EI-MS: *m/z* (%) [$M^{+\cdot}$] 333 (8) and 331 (11), [2,6–$Cl_2C_6H_3$–C≡S^+] 189 (6). [j] Cl 17.37 (17.37), S 7.88 (7.85). [k] Cl 18.93 (18.80), S 8.65 (8.50). [l] Anhydrous. [m] Cl 21.28 (21.35), S 9.86 (9.65). [n] When workup (A) was done (yield 81%). [o] 2-butanone (methyl ethyl ketone). [p] S 9.39 (9.07); EI-MS: *m/z* (%) [$M^{+\cdot}$] 353 (21). [q] EI-MS: *m/z* (%) [$M^{+\cdot}$] 353 (22).

dehydrogenated analog thiadiazole was also formed.[19w] For the pyrolysis of aldehyde thiosemicarbazones to give, among others, 5-substituted 2-amino-1,3,4-thiadiazoles[45] a free radical mechanism has been suggested.[46]

Besides the oxidant $KMnO_4$ used[21,32d] previously for the dehydrogenation of 2,5-disubstituted 3-acyl-1,3,4-thiadiazolines, also the one-electron acceptor CAN was efficiently applied for such transformations now for the first time. This method is more ready and, with more simple processing, often affords almost pure crude products in better yields in comparsion with the $KMnO_4$ oxidation (see Table 3). Also the dehydrogenation power of the charge-transfer complex forming DDQ and the hypervalent iodine oxidant IBDA were tested and found to be effective (transformations **2b**→**3b** an d **2a**→**3a**, Table 3).

It should be noted, however, that while IBDA has been reported[47] to transform aldehyde acylhydrazones into 1,3,4- oxadiazoles at room temperature within 2 minutes,[47a] it dehydrogenated 5-acetamido-3-acetyl-1,3,4-thiadiazoline (**2a**) into thiadiazole (**3a**), devoid of a deprotonable *N*-iminoamide or an intermediary endocyclic secondary amine moiety, much more slowly. The transformation of the 5-acetamido (**2**) entities can be suggested to start with loss of the AcN*H* proton and then the electron rich heterocycle joins with the endocyclic nitrogen to the hypervalent iodine reaction centre. In consonance with this mechanistic hypothesis, while a treatment with IBDA in methanol solution dehydrogenated 5-acetamido thiadiazoline (**2c**) at room temperature almost completely [TLC, $CHCl_3$/MeOH (95:5)] during 3 days, under the same conditions the 5-acetanilido analog (**2d**) resisted transformation [TLC, $CHCl_3$/MeOH (95:5)] after 4 days,

Table 3. Preparation and properties of thiadiazoles (**3**)[a]

Product	Substrate (mmol)	Agent (mmol)	Solvent (mL)	Reaction temp. [°C] (time [h][b,c])	Workup[d]	Yield[%] crude (pure)
3a	**2a** (0.5)	$KMnO_4$ (1.85)	AcOH(10) H_2O (3)	< 20 (1.5; 3)	F, C, E	70
	2a (0.5)	CAN[h] (0.967)	MeCN(10) H_2O (1)	23 (0.33; 0.75)	G, A	94.5
	2a (0.5)	IBDA[i] (0.55)	MeOH (15)	23 (2; 36)	A	93
3b	**2b** (2)	$KMnO_4$ (5)	AcOH (20) H_2O (3)	< 20 (1; 1.5)	F, G, A	81
	2b (1)	CAN (2.08)	MeCN (10) H_2O (3)	23 (0.15; 0.1)	G, A	98.5
	2b (0.5)	DDQ[o] (0.6)	PhH (5)	bp (6)	A, K	85
3c	**2c** (1)	$KMnO_4$ (2.5)	AcOH (10) H_2O (3)	< 20 (1.5; 1)	F, G, A	77.5
	2c (1)	CAN (1.7)	MeCN (10) H_2O (1)	23 (0.13; 0.5)	G, A	84
3d	**2d** (1.5)	CAN (2.63)	MeCN (30) H_2O (1.5)	23 (0.2; 0.33)	G, A	97 (88)
3e	**2e** (1)	$KMnO_4$ (2.5)	AcOH (12) H_2O (2)	< 20 (1.2; 1.5)	F, G, A	84
3g	**2g** (2)	$KMnO_4$ (5)	AcOH (15) H_2O (3)	< 20 (1; 2)	F, G, A	35 (31)
	2g (1)	CAN (2.03)	MeCN (5) H_2O (1.5)	23 (0.6; 0.17)	G, A	64 (52)

Table 3. Preparation and properties of thiadiazoles (**3**)[a] (continued)

Product	Mp [°C] (solvent)	Lit. mp [°C] (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
3a	330[e,f]	322–324 (EtOH)[g]				
	331[e,f]		$C_{10}H_8N_3OClS$	47.31	3.18	16.65
	335($CHCl_3$)[f]		(253.7)	(47.34)	(3.18)	(16.56)
	333[e,f]					
3b	>360[e]		$C_{10}H_8N_4O_3S$	45.19	3.00	20.89[j]
	>360 (DMSO/H_2O)		(264.3)	(45.45)	(3.05)	(21.20)
	>360[e]					
	>370[e]					
3c	258–259[e]		$C_{10}H_7N_3OCl_2S$	42.02	2.74	14.67[k]
	260 (EtOH)		(288.2)	(41.68)	(2.45)	(14.58)
	258[e]					
	259 ($CHCl_3$/EtOAc)					
3d	208[e]		$C_{16}H_{11}N_3OCl_2S$	52.66	2.95	11.42[l]
	208($CHCl_3$/EtOAc)		(364.3)	(52.75)	(3.04)	(11.54)
3e	298[e]		$C_{10}H_6N_4O_3Cl_2S$	35.90	1.90	16.88
	298 (DMF/H_2O)		(333.2)	(36.05)	(1.82)	(16.82)
3g	253–254[e]	251[m]	$C_{13}H_{15}N_3O_4S$	50.87	5.09	13.54[n]
	255 (AcOH/H_2O)	(EtOH)	(309.3)	(50.47)	(4.89)	(13.58)
	255 (AcOH/H_2O)					

[a] For general method of preparation see EXPERIMENTAL. [b] Input. [c] Additional reaction time. [d] For general operations of processing the reaction mixtures see EXPERIMENTAL. [e] Crude product. [f] Volatile near the melting point. [g] Ref. 58. [h] Ceric ammonium nitrate. [i] Iodobenzene diacetate: $PhI(OAc)_2$. [j] S 12.50 (12.13). [k] Cl 24.44 (24.61), S 11.50 (11.13). [l] Cl 19.56 (19.47), S 9.08 (8.80). [m] Ref. 59. [n] S 10.69 (10.37). [o] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

and only scarcely traces of the thiadiazole (**3d**) could be detected. Similary to the dehydrogenations **2**→**3**, treatment of the 2-monosubstituted fused Δ^4-thiadiazoline (**8**) with $KMnO_4$, or more advantageously with CAN, led to the formation of the thiadiazolylbenzoic acid derivative (**9**) (see EXPERIMENTAL). However, treatment of the dialdehyde derivative bithiadiazoline **10a** with $KMnO_4$, CAN or $PhI(OAc)_2$ (IBDA) did not afford the corresponding 5,5′-diacetamido-2,2′-bi[1,3,4]thiadiazole as expected, but instead 2-acetamido[1,3,4]thiadiazole *via* cleavage of the C(2)—C(2′) bond. Although CAN oxidation of 2,2′-disubstituted 3-acetyl[1,3,4]thiadiazolines was found[35] to regenerate the carbonyl group of the parent ketone (see also INTRODUCTION), treatment of the 1,2- keto aldehyde derivative

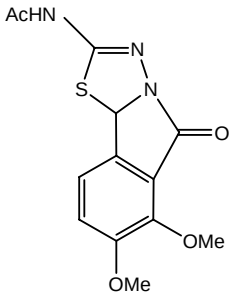
Table 4. Characteristic ^{1}H NMR spectral data[a] of thiosemicarbazones (**1**), thiadiazolines (**2**), and thiadiazoles (**3**)

Compound	δ [ppm]			
	N*H*/O*H*	C*H*=N	S–C*H*(Ar)–N	CH_3
1a		8.02[b]		
1b		8.11[b]		
1c	11.77	8.32		
	8.42			
	7.46			
1d	12.19	8.43		
1e	11.86	8.30		
	8.47			
	7.62			
1g	11.84	8.11		3.96[c]
	8.39			3.81
	8.25			
1h	11.32	8.41		3.96
	8.14			3.94[c]
	7.26			
2a			6.82[b]	
2b	11.86		6.98[b]	2.27
				2.08
2c	12.50		7.30	2.14
				2.07
2d			7.37[d]	1.92
				1.75
2e	12.06		7.53	2.29
				2.23
2f	11.81		6.81	2.20
				2.05
2g	12.19		6.92	3.89[c,e]
				3.78[e]
				2.37
				2.18
2h	11.59		7.05	3.76[f]
3a	12.69			2.22
3b	12.84			2.25
3c	12.90			2.37
3d				[g]2.13
3e	12.93			2.36
3g				4.03[c,e]
				3.87[e]
				2.35
				[g]2.68[h]

[a] 200 MHz, for solutions in [DMSO-d_6] if not otherwise stated *before* the columns. [b] Ref. 32a, for **2b** δ = 6.95. [c] 6 H. [d] Presumably; superimposed on the signals of aromatic hydrogens. [e] OMe. [f] 9 H; 3 MeO. [g] For solutions in $CDCl_3$. [h] 360 MHz.

bithiadiazoline (**10b**) with CAN did not provide 5-acetamido-2-acetyl[1,3,4]thiadiazole but 5-acetamido-2-methyl[1,3,4]thiadiazole likewise with C(2)—C(2′) bond cleavage (see EXPERIMENTAL).

CAN oxidation has been reported to transform thiocarboxamides into their oxygen analogs[48a,b] and/or into 1,2,4-thiadiazoles.[48a] Quite recently C—C bond cleavages of radical cations, obtained by photolysis of C-4 analog cyclic *N*,S-acetals 2-substituted benzothiazolines, have been thoroughly investigated.[48c]



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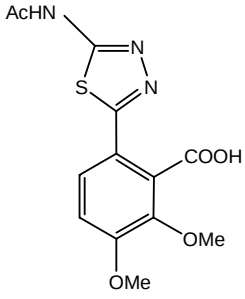

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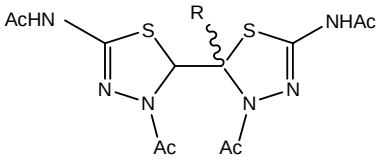

10a R=H, **10b** R=Me

Table 5. Characteristic 50 MHz ^{13}C NMR spectral data of thiadiazolines (**2**) for solutions in [DMSO-d_6]

Compound	δ [ppm]			
	C=O	S–*C*(R^7)=N	S–*C*(Ar)H–N	*C*H$_3$
2c	169.56		63.34	22.35
	167.43			21.62
2d	170.38	148.07	65.66	23.26
	168.87			21.23
2f	169.40	145.82	64.68	22.40
	167.55			21.67

Table 6. Preparation and properties of thiosemicarbazones (**6**)

Product	Reaction components (mmol)	Solvent (mL)	Reaction temp. [°C][a] (time [h])	Workup[b]	Yield[%] crude[c] (pure)[c]
6a	**5a** (30) TSC (60)	EtOH[d,e] (200)	bp (22)	C, H	99.5 (69)
6b	**5b** (30) TSC (60)	EtOH[d,e] (200)	bp (20)	I, C	~ 100 (76)
6c	**5c** (60) TSC (72)	H_2O[j] (500)	bp (3)	A[k]	98 (92)
6d	**5d** (30) TSC (60)	EtOH[d,e] (300)	bp (44)	C, J	90
6f	**5f** (10) TSC (15)	MeOH[q] (25)	bp (4)	A	95 (71)

Table 6. Preparation and properties of thiosemicarbazones (**6**) (continued)

Product	Mp [°C] (solvent)	Lit. mp [°C] (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
6a	190[f] 198 (EtOH)	202[g] (EtOH)	$C_9H_{10}N_3ClS$ (227.7)	47.34 (47.47)	4.27 (4.43)	18.63[h] (18.45)
6b	195[f] 199–200 (80% EtOH)	204[i] (aq. H_2O)	$C_9H_{10}N_3BrS$ (272.2)	39.58 (39.71)	3.65 (3.70)	15.52 (15.44)
6c	161–162[f] 162 (H_2O)[l]	161[m] (EtOH)	$C_8H_{10}N_4S$ (194.3)	49.92 (49.46)	5.36 (5.19)	28.94[n] (28.84)
6d	220[f] 221 (EtOH)	222[o] (EtOH)	$C_9H_{11}N_3O_2S$ (225.3)	48.29 (47.98)	5.08 (4.92)	18.97[p] (18.65)
6f	221[f] 221 (MEE/H_2O)[r]	226–227[s] (50% EtOH)	$C_{10}H_{10}N_4S$ (218.3)	55.36 (55.02)	4.65 (4.62)	25.76 (25.67)

TSC = thiosemicarbazide. [a] Bath if not bp. [b] For general operations of processing the reaction mixtures see EXPERIMENTAL. [c] Without workup of the mother liquors. [d] Commercial anhydrous. [e] In the presence of cc. HCl (1.5 mL). [f] Crude product. [g] Ref. 60; 86 °C (sic!; EtOH), ref. 61. [h] Cl 15.90 (15.57), S 14.25 (14.08). [i] Ref. 60; 201–202 °C (MeOH), ref. 1g; 202–203 °C (corr., 40–60% EtOH), ref. 53. [j] To a hot solution of TSC in water containing 4.8 mL AcOH was added **5c**. [k] The mother liquor was concentrated and the residue was crystallized from water. [l] The product was dried at 100 °C/0.1 Torr over P_4O_{10}. [m] Ref. 62; 158–160 °C (EtOH), ref. 63; 158–160 °C (MeOH), ref. 64; 195 °C (H_2O), ref. 65. [n] S 16.95 (16.51). [o] Ref. 66; 212–215 °C (corr.; 40–60% EtOH), ref. 53. [p] S 14.41 (14.23). [q] Containing 0.5 mL AcOH. [r] 2-Methoxyethyl ether with addition of water to the hot solution. [s] Ref. 67; 230–232 °C (MeOH), ref. 68; 265 °C, ref. 57; 208 °C (MeOH or EtOH), ref. 69.

Table 7. Preparation and properties of thiadiazolines (**7**)

Product	Substrate (mmol)	Agents (mmol)	Reaction temp. [°C][a] (time [h])	Workup[b]	Yield[%] crude (pure)[c]
7a	**6a** (15)	Ac_2O (212) py[d] (247)	100 (5)	C, D	93 (70)
7b	**6b** (30)	Ac_2O (424) py[d] (247)	100 (5)	C, E	100 (84)
7c	**6c** (25)	Ac_2O (530) py[d] (124)	100 (5.5)	C, D	81 (75)
7e	**6d** (67)	Ac_2O (1060) py[d] (927)	100 (5.5)	C, E	(83)
7g	**6f** (18)	Ac_2O (318) py[d] (247)	100 (4)	C, E	91 (58)

Table 7. Preparation and properties of thiadiazolines (**7**) (continued)

Product	Mp [°C] (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
7a	214–216[e] 220–221 ($CHCl_3$/EtOAc)	$C_{13}H_{14}N_3O_2ClS$ (311.8)	49.94 (50.08)	4.58 (4.53)	13.45[f] (13.48)
7b	218–219 ($CHCl_3$/EtOAc)	$C_{13}H_{14}N_3O_2BrS$ (356.2)	43.63 (43.83)	4.05 (3.96)	11.76[g] (11.79)
7c	219[e] 220 (ME/H_2O)[h]	$C_{12}H_{14}N_4O_2S$ (278.3)	52.06 (51.78)	5.09 (5.07)	20.11[i] (20.13)
7e	189 ($CHCl_3$/EtOAc)	$C_{17}H_{19}N_3O_6S$ (393.4)	51.96 (51.90)	5.09 (4.87)	10.42[j] (10.68)
7g	165−166 (EtOH)[k]	$C_{16}H_{16}N_4O_3S$ (344.4)	55.65 (55.80)	4.82 (4.68)	16.37[l] (16.27)

[a] Bath if not bp. [b] For general operations of processing the reaction mixtures see EXPERIMENTAL. [c] Without workup of the mother liquors. [d] Anhydrous. [e] Crude product. [f] Cl 11.73 (11.37), S 10.58 (10.28). [g] Br 23.13 (22.43), S 9.20 (9.00). [h] 2-Methoxyethanol, with adition of water. [i] S 11.53 (11.52). [j] S 8.24 (8.15). [k] Commercial anhydrous. [l] The product was dried at 100 °C/0.1 Torr over P_4O_{10}; S 9.62 (9.31); EI-MS: *m/z* (%) [$M^{+\cdot}$] 344 (3), 302 (5). Treatment with boiling Ac_2O for 4 h has been reported (ref. 70) to transform **6f** into **7f** [$C_{14}H_{14}N_4O_2S$ (302.3), the diacetyl analog of **7g**, with free indole NH].

Table 8. Characteristic 200 MHz ^{1}H- and 50 MHz ^{13}C NMR spectral data[a] of thiadiazolines (**7**)

Compound	δ [ppm] ^{1}H		^{13}C		
	N*H*	C*H*$_3$	*C*=O	*C*-2[b]	C*H*$_3$
7a	[c]10.93	2.33	[c]169.19	78.24	26.25
		2.24	168.06		23.29
		2.05			22.21
7b	10.29	2.33	169.25[d]	79.11	26.57
		2.30			23.64
		1.84			22.49
7c	[e]11.67	2.30	[e]169.30	79.67	25.87
		2.20	167.99		23.37
		2.02			22.31
7e	10.88	2.30	170.00	75.60	27.95
		2.24	168.89		23.15
		2.22	168.35		22.23
		2.18	168.02		20.86
		1.76			20.75
7g[f]	[e]11.11	2.15	[e]169.25[d]	60.88	22.61[d]
		2.09	167.12		21.96
		2.06			

[a] For solutions in $CDCl_3$ if not otherwise stated *before* the first column. [b] C-2 of the thiadiazoline ring. [c] For solution in $CDCl_3$ + [DMSO-d_6]. [d] 2 C. [e] For solution in [DMSO-d_6]. [f] The signal of S–C*H*R–N is superimposed on those of the indole hydrogens at δ = 7.49–6.97.

EXPERIMENTAL

Melting points (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (< 50 °C, bath). TLC: Kieselgel 60 F_{254} (Merck, Alurolle). IR (KBr disks): Perkin-Elmer 16 PC-FT and Perkin-Elmer 283 B spectrophotometers. 200 MHz ^{1}H- and 50 MHz ^{13}C NMR: Bruker WP 200 SY, 360 MHz ^{1}H- and 90 MHz ^{13}C NMR: Bruker AM 360 spectrometers; for recording the ^{13}C spectra, *J*-echo techniques were used. MS: VG-7035 GC/MS/DS instrument (ion current 0.1 mA, direct insertion technique, 70 eV).

General Operations of Processing the Reaction Mixtures (see Tables 1–3,6,7) (A) The product was filtered off in the cold. (B) The cold reaction mixture was poured into ice and water. (C) The reaction mixture was concentrated. (D) The cold residue was triturated with a small amount of anhydrous EtOH and kept at room temperature for 0.5–1 h, then hexane was added. (E) The cold residue was triturated with ice/water. (F) Under ice/water cooling, to the stirred reaction mixture was added 30% H_2O_2 in small portions until discoloration was complete. (G) The mixture was diluted with 2–3-fold volume of water. (H) To about a quarter. (I) The hot solution was filtered. (J) The residue was extracted with water on a steam bath to remove unreacted thiosemicarbazide. (K) The solid was stirred with aq. $NaHCO_3$ to leave the crude product undissolved.

General Procedure for $KMnO_4$ Oxidation (see Table 3) With a slight modification of the literature method[32d,7l] to a stirred and cooled suspension of the finely powdered substrate in 99% AcOH were added finely powdered $KMnO_4$ in small portions, and water in 3–4 portions. For processing the reactions mixtures see the indications in Table 3 and the General Operations (see above).

General Procedure for CAN Oxidation (see Table 3)
To a stirred suspension/solution of the powdered substrate in MeCN were added CAN in small portions (the proper time intervals being indicated by the change of color) and water in 3–4 portions. For processing the reaction mixtures see the indications in Table 3 and the General Operations (above).

Thermal Dehydrogenation of 3-Acetylthiadiazoline (2b) to Thiadiazole (3b). Thiadiazoline (**2b**) (1.3290 g, 4.31 mmol; mp 228.5 °C) was kept at 245–260 °C (bath) for 30 min (after temporary sparkling the melt resolidified; loss of weight 0.3000 g, i.e. 69.6 mg/mmol). The cold residue was triturated with 2-PrOH to give crude (1.0013 g, 87.9%) or recrystallized **3b** (0.4578 g, 40.2%), mp > 365 °C (from DMSO). The product kept at 100 °C/0.5 Torr over P_4O_{10} for 8 h was identical in all respects [mp, TLC, IR(KBr) and ^{1}H NMR (DMSO-d_6) spectrum] with that obtained by $KMnO_4$, CAN or DDQ dehydrogenations (see Table 3).

6-(5-Acetamido-1,3,4-thiadiazol-2-yl)-2,3-dimethoxybenzoic Acid (9).

Procedure A. To a stirred suspension of the finely powdered thiadiazoline lactam[49] (**8**) (9.219 g, 30 mmol) in AcOH (225 mL) was added powdered $KMnO_4$ (11.850 g, 75 mmol) in small portions during 25 min at 15–16 °C. The mixture was stirred for 10 min then H_2O (37 mL) was added in portions during 20 min. The mixture was stirred at 11–13 °C for an additional 100 min, then under further cooling ~30% H_2O_2 (~5.5 mL) was added in small portions until the decomposition of the excess $KMnO_4$ was complete and the colorless solution was concentrated. The solid residue was extracted with aq. $NaHCO_3$ (3.60 g, ~43 mmol in 50 mL H_2O) at 50–55 °C and filtered. The filtrate was acidified with concd HCl to Congo Red and kept at 5 °C for 2–3 h to obtain crude (2.672 g, 27.5%) or recrystallized **9** (2.115 g, 21.8%), mp 269 °C (from AcOH). *Anal*. Calcd for $C_{13}H_{13}N_3O_5S$: C 48.29; H 4.05; N 13.00; S 9.92. Found: C 48.26; H 4.24; N 12.98; S 10.00. IR (cm^{-1}): 3161, 2938, 2786, 1730, 1702, 1596, 1552. ^1H NMR (200 MHz, DMSO-d_6): δ 12.61 (s, 1 H, exchangeable with D_2O, NH), 7.55 and 7.23 (each d, 1 H, J = 8 Hz, 2 H, H–Ar), 3.91 and 3.78 (each s, 3 H; 2 MeO), 2.21 (s, 3 H, Ac).

Procedure B. To a stirred suspension of the powdered thiadiazoline lactam[49] (**8**) (0.0768 g, 0.25 mmol) in MeCN (4 mL) were added water (0.8 mL) and CAN (0.291 g, 0.531 mmol) in small portions during 30 min at rt. The mixture was concentrated and the residue triturated with water to furnish crude (0.0652 g, 80.7%) or recrystallized **9** (0.040 g, 49.5%), mp 265–267 °C (from AcOH with addition of water), identical [TLC, 20 mL $CHCl_3$/MeOH (7:3) + 6 drops of AcOH, as well as IR(KBr) spectrum] with the product obtained in procedure A.

5,5′-Diacetamido-3,3′-diacetyl-2,2′-bi[1,3,4]thiadiazoline (10a). A mixture of glyoxal bis(thiosemicarbazone)[50] (10.00 g, 48.95 mmol), Ac_2O (50 mL) and anhydrous pyridine (20 mL) was boiled with stirring for 1 h and then cooled to give a crude product (12.39 g, 68%), mp > 365 °C . The mother liquor was poured into ice/water to afford a second crop (1.300 g, 7.1%). For analysis a sample (2.00 g) was recrystallized from DMF (23 mL) with addition of warm water (50 mL) to give the pure title compound (1.665 g). *Anal*. Calcd for $C_{12}H_{16}N_6O_4S_2$: C 38.70; H 4.33; N 22.57. Found: C 38.82; H 4.40; N 22.62. ^1H NMR (100 MHz at 330 K, DMSO-d_6) HMDSO as the internal standard: δ 11.73 (br s, 1 H, exchangeable with CD_3COOD, NH), 6.47 and 6.32 (2 s, ¾ and ¼ H, S–CHR–N), 2.28 (s, 3 H, Ac), 2.22 (s, 3 H, Ac).

Oxidative Transformation of the Bithiadiazoline (10a) into 2-Acetamido[1,3,4]thiadiazole.

Procedure A. To a stirred suspension of powdered **10a** (0.372 g, 1 mmol, 2 "mmol" of the heteroring) in AcOH (20 mL) were added powdered $KMnO_4$ (0.790 g, 5 mmol) and water (1 + 1 mL) at rt during 1 h. The reaction mixture was stirred for an additional 2 h then processed (see General Procedure as well as General Operations C, E, G) to give crude (0.090 g, 62.8%) or recrystallized (0.055 g, 38.4%)

2-acetamido[1,3,4]thiadiazole, mp 269 °C (from water), ref. 51: 268 °C (from water), ref. 19i: mp 267–268 °C (from AcOH). ^{1}H NMR (DMSO-d_6): δ 12.26 (s, 1 H, NH), 9.27 (s, 1 H, 5-H), 2.31 (s, 3 H, Ac).

Procedure B. To a stirred mixture of powdered **10a** (0.9311 g, 2.5 mmol, 5 "mmol" of the heteroring) in MeCN (60 mL) and water (12 mL) was added CAN (6.439 g, 11.51 mmol, 98%) during 30 min at rt. The reaction mixture was saturated with Na_2SO_4 and thoroughly extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$) and then concentrated. The residue was crystallized from EtOAc to give crude (0.2161 g, 60.4%) or recrystallized (0.1273 g, 39.1%) 2-acetamido[1,3,4]thiadiazole, mp 272 °C (from EtOAc; near the mp it volatilizes). MS: *m*/*z* [$M^{+\cdot}$] 143(28), [$M^{+\cdot}$ – Me] 128(7), [$M^{+\cdot}$ – N_2: 2-acetamidothiirene] 115(30), [$M^{+\cdot}$ – CH_2CO: 2-aminothiadiazole] 101(100), [$M^{+\cdot}$– CH_2CO – HCN: 3-aminothiazirene] 74(28), [$M^{+\cdot}$ – CH_2CO – H_2NCN: thiazirene] 59(9), [HC≡S^+] 45(45), in accordance with the known[52] fragmentation pattern of 2-(acyl)amino[1,3,4]thiadiazoles.

Procedure C. To a stirred suspension of powdered **10a** (1.117 g, 3 mmol, 6 "mmol" of the heteroring) in MeOH (160 mL) was added powdered IBDA (2.241 g, 6.818 mmol, 98%) at rt during 10 min. The mixture was stirred for 5 d (the oxidant was consumed: KI/starch paper), filtered and concentrated. The residue was extracted with $CHCl_3$ (~350 mL) and the solution washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), treated with fuller's earth and charcoal, and then concentrated. The residue was boiled in EtOAc (30 mL) to give the TLC-homogeneous pure title thiadiazole (0.3595 g, 83.7%, calcd for 3 mmol), mp 272–273 °C.

Degradation of 5,5′-Diacetamido-3,3′-diacetyl-2′-methyl-2,2′-bi[1,3,4]thiadiazoline (10b) to 2-Acetamido-5-methyl-1,3,4-thiadiazole. To a stirred suspension of the powdered bithiadiazoline (**10b**)[41f] (0.773 g, 2 mmol, 4 "mmol" of the heteroring) in MeCN (50 mL) and water (10 mL) was added CAN (4.984 g, 8.91 mmol, 98%) during 30 min. The mixture was neutralized with $NaHCO_3$ and concentrated. The residue was extracted several times with hot $CHCl_3$. The combined $CHCl_3$ solution was washed with water, dried ($MgSO_4$) and then concentrated. The residue was crystallized from EtOAc to give homogeneous [TLC, $CHCl_3$/MeOH (95:5)] 2-acetamido-5-methyl-1,3,4-thiadiazole (0.131 g, 41.7%), mp 294–296 °C, ref. 44c: 293 °C (from aq. NaOH with addition of HCl), ref. 51: 292 °C (from water). IR (cm^{-1}): 3170, 3040, 2914, 2796, 1696, 1570. MS: *m*/*z* [$M^{+\cdot}$] 157(18), [$M^{+\cdot}$ – Me] 142(15), [$M^{+\cdot}$ – CH_2=CO] 115(85), [2-aminothiadiazole?] 101(8), [$M^{+\cdot}$ – CH_2=CO – MeCN = 3-aminothiazirene] 74(45), [thiazirene and/or Me–C≡S^+] 59(25); 56(22), [Me–C≡O^+] 43(100), in accordance with the known[52] fragmentation pattern of 2-amino-1,3,4-thiadiazoles. $C_5H_7N_3OS$ (157.2).

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REFERENCES

1. a) V. V. Alekseev and K. N. Zelenin, *Chem. Heterocycl. Compd*., (1998, pub.1999, N. Y.), **34**, 919 (*Chem. Abstr*., 1999, **130**, 282270q); b) S. I. Yakimovich, I. V. Zerova, and K. N. Zelenin, *Ross. Khim. Zh.,* 1999, **43**, 115, and references cited therein (*Chem. Abstr*., 1999, **131**, 44442y); c) R. E. Valters, F. Fülöp, and D. Korbonits, *Adv. Heterocycl. Chem*., 1996, **66**, 1; d) K. N. Zelenin, V. V. Alekseev, O. B. Kuznetsova, P. B. Terentyev, V. V. Lashin, V. V. Ovcharenko, and L. A. Khorseeva, *Zh. Org. Khim*., 1993, **29**, 278 (*Chem. Abstr*., 1994, **120**, 270964z); e) K. N. Zelenin, V. V. Alekseyev, O. B. Kuznetsova, V. N. Torocheshnikov, and L. A. Khorseeva, *Tetrahedron*, 1993, **49**, 5327; f) K. N. Zelenin and V. V. Alekseev, *Khim. Geterotsikl. Soedin*., 1992, 851 (*Chem. Abstr*., 1993, **118**, 147485a); g) K. N. Zelenin, O. B. Kuznetsova, P. B. Terentyev, V. N. Torocheshnikov, and V. V. Lashin, *Khim. Geterotsikl. Soedin*., 1992, 1689 (*Chem. Abstr*., 1993, **119**, 138566w); h) K. Toyooka, Y. Takeuchi, H. Ohto, M. Shibuya, and S. Kubota, *Chem. Pharm. Bull*., 1991, **39**, 777; i) K. Toyooka, Y. Takeuchi, Z. Taira, and S. Kubota, *Heterocycles*, 1989, **29**, 1233; j) K. N. Zelenin, V. V. Alekseev, O. V. Solod, O. B. Kuznetsova, and V. N. Torocheshnikov, *Dokl. Akad. Nauk. SSSR,* 1987, **296**, 1133 (*Chem. Abstr*., 1988, **109**, 22400b); k) L. Mester, Derives Hydraziniques des Glucides. Hermann, Paris, 1967, pp. 179.
2. M. A. Martins Alho and N. B. D'Accorso, *Carbohydr. Res*., 2000, **328**, 481.
3. J. R. Holker, *Chem. Ind*. (*London*), 1964, 546.
4. F. V. Pishchugin, Z. Sh. Sharshenalieva, A. Ya. Ott, and A. A. Aleksandrova, *Izv. Akad. Nauk Kirg. SSR*, 1978, 54 (*Chem. Abstr*., 1978, **89**, 110143u).
5. S. Kabashima, T. Okawara, T. Yamasaki, and M. Furukawa, *Heterocycles*, 1990, **31**, 1129.
6. a) C. A. Mugford and J. B. Tarloff, *Drug Metab. Dispos*., 1995, **23**, 290 (*Chem. Abstr*., 1995, **122**, 122480q); b) B. Lenkey and L. Somogyi, *Acta Microbiol. Immunol. Hung*., 1996, **43**, 263; c) M. M. Salunkhe and R. V. Nair, *J. Mol. Catal. B: Enzym*., 2000, **10**, 535 (*Chem. Abstr*., 2000, **133**, 349958c); d) T. Mino, T. Matsuda, D. Hiramatsu, and M.Yamashita, *Tetrahedron Lett*., 2000, **41**, 1461; e) Raunak, A. K. Prasad, N. A. Shakil, Himanshu, and V. S. Parmar, *Pure Appl. Chem*., 2001, **73**, 167; f) R. J. MacCracken and D. G. Kennedy, *J. Chromatogr. B*, 1997, **691**, 87; g) R. J. MacCracken, D. E.

Spence, S. D. Floyd, and D. G. Kennedy, *Food Additives and Contaminants*, 2001, **18**, 954 (*Chem. Abstr*., 2002, **136**, 19259q); h) W. Leitner, P. Zöllner, and W. Lindner, *J. Chromatogr. A*, 2001, **939**, 49.

7. a) H. El Khadem, M. A. E. Shaban, and M. A. M. Nassr, *Carbohydr. Res*., 1970, **13**, 470; b) H. El Khadem, M. Shaban, and M. Nassr, *Carbohydr. Res*., 1972, **23**, 103; c) C. E. Cannizzaro, I. M. E. Thiel, and N. B. D'Accorso, *J. Heterocycl. Chem*., 1998, **35**, 481; d) N. Linganna and K. M. L. Rai, *Synth. Commun*., 1998, **28**, 4611, and references cited therein.
8. a) W. Krasuski and M. Regitz, *Z. Naturforsch*., 1984, **39B**, 1806; b) A. B. Tomchin, *Russ. J. Org. Chem*., 1997, **33**, 567 (*Chem. Abstr*., 1998, **128**, 192597f).
9. a) P. Rademacher, *Adv. Heterocycl. Chem*., 1998, **72**, 361; b) F. Jin and P. N. Confalone, (Du Pont Pharmaceuticals Company, USA), PCT Int. Appl. WO 99 26, 945 (3 Jun 1999) (*Chem. Abstr*., 1999, **131**, 19015d); c) X.-J. Zou, L.-H. Lai, G.-Y. Jin, and Z.- X. Zhang, *J. Agric. Food Chem*., 2002, **50**, 3757.
10. a) J. Sandström, *Adv. Heterocycl. Chem*., 1968, **9**, 165; b) A. Lawson and R. B. Tinkler, *Chem. Rev*., 1970, **70**, 593; c) M. M. Campbell, in *Comprehensive Organic Chemistry* (*the Synthesis and Reactions of Organic Compounds*), ed. by D. Barton, W. D. Ollis, and P. G. Sammes, Vol. 4, p. 1033, Pergamon Press, Oxford, 1979; d) A. S. Shawali and C. Párkányi, *J. Heterocycl. Chem*., 1980, **17**, 833; e) G. Kornis, in *Comprehensive Heterocyclic Chemistry* ed. by A. R. Katritzky, Ch. W. Rees, and K. T. Potts, Vol. 6, p. 545, Pergamon Press, Oxford, 1984; f) R. Tanaka and I. Shinkai, *Prog. Heterocycl. Chem*., 1992, **4**, 123; g) P. J. Steel, *Adv. Heterocycl. Chem*., 1996, **67**, 1; h) P. A. Bradley and D. J. Wilkins, *Prog. Heterocyc. Chem*., 1997, **9**, 170; 1998, **10**, 172; 1999, **11**, 184; i) A. D. Garnovskii and A. P. Sadimenko, *Adv. Heterocycl. Chem*., 1998, **72**, 1.
11. a) F. M. E. Abdel-Megeid, M. A.-F. Elkaschef, and H. M. A. Abdel-Bary, *Carbohydr. Res*., 1977, **59**, 95, and references cited therein; b) W. B. Cowden, S. J. Sullivan, and D. J. Brown, *Aust. J. Chem*., 1985, **38**, 1257, and references cited therein; c) J. Dixon and D. H. Robinson, (Fisons PLC) Brit. UK Pat. Appl. GB 2,179,655 (11 Mar 1987) (*Chem. Abstr*., 1988, **108**, 37839e); d) S. Farooq, J. Ehrenfreund, and H. R. Waespe, (Ciba-Geigy A.-G.), Eur. Pat. Appl. EP 274, 988 (20 July 1988) (*Chem. Abstr*., 1988, **109**, 149550f); e) T. A. Blumenkopf, T. Spector, D. R. Averett, R. W. Morrison Jr., E. C. Bigham, and V. L. Styles, (Wellcome Foundation Ltd.), Eur. Pat. Appl. EP 349, 243 (03 Jan 1990) (*Chem. Abstr*., 1990, **112**, 235185j); f) E. Beriger and W. Eckhardt, (Ciba-Geigy A.-G.), Eur. Pat. Appl. EP 364, 396 (18 Apr 1990) (*Chem. Abstr*., 1990, **113**, 152432g); g) G. D. S. A. Jayaweera, S. A. MacNeil, S. F. Trager, and G. M. Blackburn, *Bioorg. Med. Chem. Lett*., 1991, **1**, 407; h) M. T. Reamer, W. A. Spitzer, and F. Victor, (Lilly, Eli, and Co.), Eur. Pat. Appl. EP 392, 769 (17 Oct 1990) (*Chem. Abstr*., 1991, **114**, 229307a); i) M. E. Zuhair, A. Abu-Al-Teman, F. A. Hussein, S. R. Salman,

D. Al-Dujaili, and V. F. Roche, *Eur. J. Med. Chem*., 1992, **27**, 93; j) S. Antonaroli, A. Bianco, M. Brufani, L. Cellai, G. Lo Baido, E. Potier, L. Bonomi, S. Perfetti, A. I. Fiaschi, and G.Segre, *J. Med. Chem*., 1992, **35**, 2697; k) M. D. Mullican, M. W. Wilson, D. T. Conner, C. R. Kostlan, D. J. Schrier, and R. D. Dyer, *J. Med. Chem*., 1993, **36**, 1090; l) M. A. Hanna, M. M. Girges, D. Rasala, and R. Gawinecki, *Arzneim.- Forsch./Drug Res*., 1995, **45(II)**, 1074; m) M. G. Mamolo, L. Vio, and E. Banfi, *Farmaco*, 1996, **51**, 71; n) N. Ulusoy, N. Ergenc, and G. O. Sanis, *Acta Pharm. Turc*., 1996, **38**, 111 (*Chem. Abstr*., 1997, **126**, 59917c); o) M. K. Srivastava, R. K. Khare, and H. Singh, *Bull. Pol. Acad. Sci.: Biol. Sci.,* 1995, publ. 1996, **43**, 113 (*Chem. Abstr*., 1997, **126**, 44810p); p) M. Barboiu, M. Cimpoesu, C. Guran, and C. T. Supuran, *Met.-Based Drugs*, 1996, **3**, 227 (*Chem. Abstr*., 1997, **126**, 126063m); q) H. Hori, N. Noguchi, H. Yokoyama, H. Ise, C.-Z. Jin, S. Kasai, T. Goto, and Z. Taira, *Bioorg. Med. Chem*., 1996, **4**, 247; r) L. V. G. Nargund, G. R. N. Reddy, and V. Hariprasad, *Indian J. Chem., Sect. B:Org. Chem. Incl. Med. Chem*., 1996, **35B**, 499 (*Chem. Abstr*., 1996, **125**, 33502t); s) U. Mishra, A. Hitkari, A. K. Saxena, S. Gurtur, and K. Shanker, *Eur. J. Med. Chem*., 1996, **31**, 629; t) C. T. Supuran and B. W. Clare, *Eur. J. Med. Chem*., 1999, **34**, 41, and references cited therein; u) S. R. Turner and S. Thaisrivongs, (Pharmacia and Upjohn Company, USA), PCT Int. Appl. WO 99 47, 507 (23 Sep 1999) (*Chem. Abstr*., 1999, **131**, 243271s).

12. a) A. Varvaresou, A. Tsantili-Kakoulidou, Th. Siatra-Papastaikoudi, and E. Tiligada, *Arzneim.-Forsch./Drug Res*., 2000, **50(I)**, 48, and references cited therein; b) C. D. Supuran and A. Scozzafava, *Eur. J. Med. Chem*., 2000, **35**, 867; c) J. J. Takasugi and B. L. Buckwalter, (American Cyanamide Company, USA), Eur. Pat. Appl. EP 1,004,241 (31 May 2000) (*Chem. Abstr*., 2000, **133**, 1761a); d) T. Inoue, K. Iwai, M. Murata, S. Nishinaka, M. Aoki, and H. Kawakami, (Sumitomo Pharmaceuticals Co., Ltd,; Sumitomo Chemical Co., Ltd.; Japan) Jpn. Kokai Tokkyo Koho JP 2000, 229, 959 (22 Aug 2000) (*Chem. Abstr*., 2000, **133**, 177177d); e) A. Foroumadi, M. Mirzaei, and A. Shafiee, *Pharmazie*, 2001, **56**, 610; f) F. Clerici, D. Pocar, M. Guido, A. Loche, V. Perlini, and M. Brufani, *J. Med Chem.,* 2001, **44**, 931; g) J. J. Takasugi and B. L. Buckwalter, (American Cyanamid Company, USA) U.S. US 6,235,762 (22 May 2001) (*Chem. Abstr*., 2001, **134**, 362770a).
13. a) E. Winkelmann and H. Rolly, *Arzneim.-Forsch./ Drug Res*., 1972, **22**, 1704; b) A. C. Fabretti, G. C. Franchini, and G. Peyronel, *Transition Met. Chem.* (*Weinheim*), 1982, **7**, 306; c) K. S. Siddiqi, M. A. A. Shah, V. Islam, and S. A. A. Zaidi, *Indian J. Chem., Sect. A*, 1983, **22A**, 355 (*Chem. Abstr*., 1983, **99**, 11778e); d) M. J. Hudson and M. J. Shepherd, (Re- Chem International Ltd.), Brit. UK Pat. Appl. GB 2,096,131 (13 Oct 1982) (*Chem. Abstr*., 1983, **98**, 111394z); e) A. C. Fabretti and G. Franchini, *Transition Met. Chem*. (*Weinheim, Ger*.), 1984, **9**, 190; f) K. C. Satpathay, B. B. Jal, and R. Mishra, *Indian J. Chem*., 1986, **25A**, 196 (*Chem Abstr*., 1986, **105**, 17081m); g) G. Meng and L. Xu, *Zhongguo Yaowu Huaxue Zazhi*, 1996, **6**, 257 (*Chem. Abstr*., 1997, **127**, 220601c); h) A. V. Kudrik,

M. K. Islyaikin, and R. P. Smirnov, *Zh. Obshch. Khim*., 1996, **66**, 1564 (*Chem. Abstr*., 1997, **126**, 144264g); i) K. Xu, Z. Zuo, and L. Yu, *Hecheng Huaxue*, 1997, **5**, 45 (*Chem. Abstr*., 1997, **127**, 293175b); j) R. Olar, D. Marinescu, C. Popescu, and C. T. Supuran, *Rev. Roum. Chim*., 1997, **42**, 111 (*Chem. Abstr*., 1997, **127**, 214056n); k) C. T. Supuran, A. Scozzafa, L. Menabuoni, F. Mincione, F. Briganti, and G. Mincione, *Met.-Based Drugs*, 1999, **6**, 67 (*Chem. Abstr*., 1999, **131**, 96443u); l) Z. Wu and H. Ma, *Huaxue Shijie*, 1999, **40**, 413 (*Chem. Abstr*., 2000, **132**, 122705y); m) M. Biagini Cingi, M. Lanfranchi, M. A. Pellinghelli, and M. Tegoni, *Eur. J. Inorg. Chem*., 2000, 703; n) M. M. Ishankhodzhaeva, M. G. Levkovich, A. B. Kozina, Sh. A. Kadyrova, and N. A. Parpiev, *Russ. J. Gen. Chem*., 2000, **70**, 1801 (*Chem. Abstr*., 2001, **135**, 170996c); o) T. Igarashi, (Fuji Photo Film Co.Ltd., Japan) Jpn. Kokai Tokkyo Koho JP 2000 26,472 (25 Jan 2000) (*Chem. Abstr.,* 2000, **132**, 129800j); p) O. A. Azizkulova and A. A. Amindzhanov, *Zh. Neorg. Khim*., 2001, **46**, 444 (*Chem. Abstr*., 2001, **135**, 131229k); q) H. Jia and L. Wang, (Peop. Rep. China) Faming Zhuanli Shenqing Gonkai Shuomingshu CN 1,292,217 (25 Apr 2001) (*Chem. Abstr*., 2001, **135**, 206893h).

14. a) M. Ohta and T. Higashijima, *J. Pharm. Soc. Jpn*., 1952, **72**, 376 (*Chem. Abstr*., 1953, **47**, 3856e); however, cf. ref. 14c; b) G. Mazzone, G. Puglisi, F. Bonina, and A. Corsaro, *J. Heterocycl. Chem*., 1983, **20**, 1399; c) E. V. P. Tao and G. S. Staten, *J. Heterocycl. Chem*., 1984, **21**, 599; d) F. Kurzer and K. M. Doyle, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1873; e) H. Wamhoff and M. Zahran, *Synthesis*, 1987, 876; f) T. Okawara, Y. Tateyama, T. Yamasaki, and M. Furukawa, *J. Heterocycl. Chem*., 1988, **25**, 1071; g) F. Kurzer and J. L. Secker, *J. Heterocycl. Chem*., 1989, **26**, 355, and references cited therein; h) E. S. M. E. Mansour, A. A. Kassem, M. E. El-Arabi, M. A. Nasser, and A. A. El-Toukhy, *Pharmazie*, 1990, **45**, 435; i) Z. Li, X. Wang, and Y. Da, *Synth. Commun*., 2000, **30**, 3971; j) Z. Szarka, R. Skoda-Földes, J. Horváth, Z, Tuba, and L. Kollár, *Steroids*, 2002, **67**, 581; k) R. Grashey, M. Baumann, and W.-D. Lubos, *Tetrahedron Lett*., 1968, 5881; l) P. Thieme, M. Patsch, and H. König, *Justus Liebigs Ann. Chem*., 1972, **764**, 94.
15. a) H. M. Hassaneen, A. H. Shetta, N. M. Elwan, and A. S. Shawali, *Heterocycles*, 1982, **19**, 1477; b) L. Belen'kii, I. Poddubny, and M. Krayushkin, *Phosphorus, Sulfur Silicion Relat. Elem*., 1994, **95**, **96**, 469 (*Chem. Abstr*., 1995, **123**, 9392v).
16. a) E. V. P. Tao and C. F. Christie Jr., *Org. Prep. Proced. Int*., 1975, **7**, 179; b) K. C. Joshi and V. K. Singh, *Pharmazie*, 1978, **33**, 254, and references cited therein; c) N. A. Kravchenya, *Khim.-Farm. Zh*., 1985, **19**, 1259 (*Chem. Abstr*., 1986, **105**, 114982p); d) S. M. Golovlyova, Yu. A. Moskvichev, E. M. Alov, D. B. Kobylinsky, and V. V. Ermolaeva, *Chem. Heterocycl. Compd*., (*New York, NY, USA), (Transl. of Khim. Geterotsikl. Soedin*.), 2001, **37**, 1102.
17. a) F. Malbec, R. Milcent, and G. Barbier, *J. Heterocycl. Chem*., 1984, **21**, 1689; b) V. I. Kelarev, R. A. Karakhanov, S. Sh. Gasanov, G. V. Morozova, and K. P. Kuatbekova, *Zh. Org. Khim*., 1993, **29**,

388.

18. a) H. Mastalerz and M. S. Gibson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 245; b) L. Koshy and C. P. Joshua, *Indian J. Chem*., 1986, **25B**, 530 (*Chem. Abstr*., 1987, **106**, 18448u); c) S. Treppendahl and P. Jakobsen, *Acta Chem. Scand*., 1977, **B31**, 264.
19. a) J. Eckenstein, E. Brogle, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta*, 1950, **33**, 1353; b) J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, and W. A. Lott, *J. Am. Chem. Soc*., 1951, **73**, 906; c) B. Holmberg, *Arkiv Kemi*, 1952, **4**, 33 (*Chem. Abstr*., 1956, **50**, 7816e); d) B. Holmberg, *Arkiv Kemi*, 1956, **9**, 65 (*Chem. Abstr*., 1956, **50**, 11322f); e) P. W. Sadler, *J. Org. Chem*., 1961, **26**, 1315; f) G. Werber and F. Maggio, *Ann. Chim. Rome*, 1961, **51**, 944 (*Chem. Abstr*., 1962, **56**, 7305f); g) G. Ramachander and V. R. Srinivasan, *J. Sci. Ind. Res*., 1962, **21C**, 44 (*Chem. Abstr*., 1962, **57**, 16600d); h) G. Ramachander and V. R. Srinivasan, *J. Sci. Ind. Res*., 1962, **21C**, 70 (*Chem. Abstr*., 1962, **57**, 4665b); i) G. Werber and F. Maggio, *Ann. Chim. Rome*, 1963, **53**, 3 (*Chem Abstr*., 1963, **59**, 6407d); j) T. Kurihara, H. Takeda, N. Iino, and T. Chiba, *Yakugaku Zasshi*, 1965, **85**, 920 (*Chem. Abstr*., 1966, **64**, 730c); k) F. Gagiu and A. Mavrodin, *Pharmazie*, 1967, **22**, 434; l) S. Toyoshima, K. Shimada, K. Kawabe, and T. Kanazawa,*Yakugaku Zasshi*, 1969, **89**, 779 (*Chem. Abstr.,* 1969, **71**, 81055n); m) K. H. Mayer and D. Lauerer, *Justus Liebigs Ann. Chem*., 1970, **731**, 142; n) G. Werber, F. Buccheri, and M. L. Marino, *J. Heterocycl. Chem*., 1975, **12**, 581; o) G. Werber, F. Buccheri, M. Gentile, and L. Librici, *J. Heterocycl. Chem*., 1977, **14**, 853; p) E. S. H. El Ashry, M. M. A. Abdel Rahman, A. Hazah, and F. Singab, *Sci. Pharm*., 1980, **48**, 13 (*Chem. Abstr*., 1980, **93**, 204523c); q) M. Valentiny and A. Martvon, *Chem. Zvesti*, 1982, **36**, 111 (*Chem. Abstr*., 1982, **97**, 6703f); r) E. S. H. El Ashry, M. A. M. Nassr, Y. El Kilany, and A. Mousaad, *J. Prakt. Chem*., 1986, **328**, 1; s) E. S. H. El Ashry, M. A. Nassr, Y. El Kilany, and A. Mousaad, *Bull. Chem. Soc. Jpn*., 1987, **60**, 3405; t) R. Noto, F. Buccheri, G. Cusmano, M. Gruttadauria, and G. Werber, *J. Heterocycl. Chem.,* 1991, **28**, 1421, and references cited therein; u) M. A. Martins Alho and N. B. D' Accorso, *J.Heterocycl. Chem*., 1997, **34**, 1415; v) R. Noto, P. L. Meo, M. Gruttadauria, and G. Werber, *J. Heterocycl. Chem*., 1999, **36**, 667; w) M. A. Martins Alho and N. B. D' Accorso, *J. Heterocycl*. *Chem*., 2000, **37**, 811; x) G. Werber, F. Buccheri, N. Vivona, and M. Gentile, *J. Heterocycl. Chem*., 1977, **14**, 1433.
20. a) A. B. Sen and S. K. Gupta, *J. Indian Chem. Soc*., 1962, **39**, 628 (*Chem. Abstr*., 1968, **69**, 10399a); b) N. C. Desai, B. R. Parekh, and K. A. Thaker, *J. Indian Chem. Soc*., 1987, **64**, 491 (*Chem. Abstr*., 1988, **109**, 37770w); c) Z. El-Gendy, R. M. Abdel-Rahman, M. M. Fawzy, and M. B. Mahmoud, *J. Indian Chem. Soc*., 1990, **67**, 927.
21. S. Y. Hassan, H. M. Faidallah, A. M. El-Massry, M. A. A. Al Haiza, and M. M. El-Sadek, *J. Saudi Chem. Soc*., 1999, **3**, 171 (*Chem. Abstr*., 2000, **132**, 321831m).
22. M. A. E. Shaban, M. F. Iskander, and S. M. El-Badry, *Pharmazie*, 1997, **52**, 350.

23. a) T. Sugawara, H. Masuya, T. Matsuo, and T. Miki, *Chem. Pharm. Bull*., 1979, **27**, 2544 and 1988, **28**, 2116; b) A. A. Hassan, *Bull. Soc. Chim. Fr*., 1994, **131**, 424; c) A. A. Hassan, Y. R. Ibrahim, A. A. Semida, and A.-F. E. Mourad, *Liebigs Ann. Chem*., 1994, 989.
24. a) N.K. Mohamed, *Phosporus, Sulfur and Silicon*, 1998, **133**, 141; b) N. K. Mohamed, *Pharmazie*, 1998, **53**, 529.
25. J. Chang, K. Zhao, and S. Pan, *Tetrahedron Lett*., 2002, **43**, 951.
26. Chandrasekhar, Ch. R. Reddy, and M. V. Reddy, *Chem. Lett*., 2000, 430.
27. N. Pathak, M. K. Goyal, M. Jain, and K. C. Joshi, *J. Indian Chem. Soc*., 1993, **70**, 539.
28. M. Takahashi and T. Yamaoka, *Heterocycl. Commun*., 1997, **3**, 521.
29. a) A. B. Tomchin, *Zh. Org. Khim*., 1981, **17**, 1561 (*Chem. Abstr*., 1981, **95**, 169091c); b) V. V. Alekseev, V. A. Khrustalev, and K. N. Zelenin, *Khim. Geterotsikl. Soedin*., 1981, 1569 (*Chem. Abstr.,* 1982, **96**, 84961g); c) D. M. Evans and D. R. Taylor, *J. Chem. Soc., Chem. Commun*., 1982, 188; d) K. N. Zelenin, V. A. Khrustalev, V. V. Alekseev, P. A. Sharbatyan, and A. T. Lebedev, *Khim. Geterotsikl. Soedin*., 1982, 904 (*Chem. Abstr*., 1982, **97**, 162877w); e) D. M. Evans, L. Hill, D. R. Taylor, and M. Myers, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1499; f) Fisons PLC, Jpn. Kokai Tokkyo Koho JP 62 53,976 [87 53,976] (09 Mar 1987) (*Chem. Abstr*., 1987, **107**, 115608z); g) E. F. V. Scriven, J. G. Keay, and T. Zhang, (Reilly Industries, Inc.), PCT Int. Appl. WO 94 07,871 (14 Apr 1994) (*Chem. Abstr*., 1994, **121**, 57536a).
30. a) V. Fülöp, A. Kálmán, A. K. Basak, M. Ghosh, and S. K. Mazumdar, *J. Mol. Struct*., 1987, **159**, 303; b) F. Buccheri, G. Cusmano, R. Noto, R. Rainieri, and G. Werber, *J. Heterocycl. Chem*., 1987, **24**, 521; c) W. Kantlehner, E. Haug, W. Kinzy, H. Hagen, P. Speh, and H.-J. Bräuner, *Chem.-Ztg*., 1989, **113**, 125 (*Chem. Abstr*., 1989, **111**, 134053p); d) U. Radics, J. Liebscher, B. Ziemer, and V. Rybakov, *Chem. Ber*., 1992, **125**, 1389; e) C. A. Montanari, J. P. B. Sandall, Z. Miyata, N. Z. Kyian, and J. Miller, *Quim. Nova*, 1993, **16**, 404 (*Chem. Abstr*., 1994, **121**, 57403e); f) V. V. Alekseev, K. N. Zelenin, P. B. Terent'ev, V. V. Lashin, L. A. Khorseeva, and G. A. Bulakhov, *Zh. Org. Khim*., 1993, **29**, 588 (*Chem. Abstr*., 1994, **120**, 322469p); g) V. V. Ovcharenko, V. V. Lashin, and P. B.Terentev, *Khim. Geterotsikl. Soedin*., 1993, 991, and references cited therein (*Chem. Abstr*., 1994, **120**, 106800v); h) K. N. Zelenin, O. B. Kuznetsova, V. V. Alekseev, P. B. Terentyev, V. N. Torocheshnikov, and V. V. Ovcharenko, *Tetrahedron*, 1993, **49**, 1257; i) K. N. Zelenin, O. B. Kuznetsova, V. V. Alekseev, I. Y. Kalvinsh, and L. Y. Leitis, *Khim. Geterotsikl. Soedin*., 1994, 119 (*Chem. Abstr*., 1994, **121**, 156895y); j) N. S. Cho, H. J. Hwang, J.-G. Kim, and I.-H. Suh, *Heterocycles*, 2001, **55**, 579.
31. a) E. I. Kazakova, V. V. Dunina, V. M. Potapov, E. G. Rukhadze, and E. Ya. Lyakhovetskaya, *Zh. Org. Khim.,* 1978, **14**, 796 (*Chem. Abstr*., 1978, **89**, 59756s); b) P. Molina, A. Arques, and M. V.

Valcarcel, *Synthesis*, 1982, 944.

32. a) S. Kubota, K. Fujikane, M. Uda, and T. Yoshioka, *Heterocycles*, 1976, **4**, 1909; b) L. Somogyi, *Symp. Pap. – IUPAC Int. Symp. Chem. Nat. Prod. 11th*, 1978, **3**, 178 (N. Marekov, and A. Orahovats, Eds., – Izd. BAN, Sofia); c) L. Somogyi, *Carbohydr. Res*., 1979, **75**, 325; d) S. Kubota, Y. Ueda, K. Fujikane, K. Toyooka, and M. Shibuya, *J. Org. Chem*., 1980, **45**, 1473; e) S. Andreae and E. Schmitz, *Z. Chem*., 1983, **23**, 450; f) Y. Nakayama and Y. Sanemitsu, *J. Org. Chem*., 1984, **49**, 1703; g) S. Andreae, E. Schmitz, and H. Seeboth, *J. Prakt. Chem*., 1986, **328**, 205; h) L. Somogyi, *Tetrahedron*, 1991, **47**, 9305, and references cited therein; i) G. C. Saha, K. Khayer, M. R. Islam, and M. S. K. Chowdhury, *Indian J. Chem., Sect. B*, 1992, **31B**, 547; j) L. Somogyi, *Liebigs Ann. Chem*., 1993, 931.
33. a) P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, 1958, **41**, 2058; b) W. R. Sherman and A. A. Alter, *J. Org. Chem*., 1962, **27**, 2237; c) D. H. Jones, R. Slack, S. Squires, and K. R. H. Wooldridge, *J. Med. Chem*., 1965, **8**, 676; d) M. P. L. Caton, D. H. Jones, R. Slack, S. Squires, and K. R. H. Wooldridge, *J. Med. Chem*., 1965, **8**, 680; e) A. Silberg and Z. Frenkel, *Bull. Soc. Chim. Fr*., 1967, 2235; f) F. Kállay, G. Janzsó, and I. Koczor, *Tetrahedron*, 1967, **23**, 4317; g) G. Doleschall and K. Lempert, *Acta Chim. Acad. Sci. Hung*., 1970, **64**, 369.
34. L. Somogyi, Gy. Batta, and A. L. Tőkés, *Liebigs Ann. Chem*., 1992, 1209.
35. L. Somogyi, Unpublished results.
36. a) R. Bognár, J. Bálint, and M. Rákosi, *Justus Liebigs Ann. Chem*., 1977, 1529; b) L. Somogyi, *Liebigs Ann. Chem.,* 1994, 959.
37. a) L. Somogyi, *Synth. Commun*., 1999, **29**, 1857; b) L. Somogyi, *Can. J. Chem*., 2001, **79**, 1159.
38. N. Naulet and G. J. Martin, *Tetrahedron Lett*., 1979, 1493.
39. L. Somogyi, *Liebigs Ann. Chem*., 1991, 1267.
40. L. Somogyi and P. Sohár, *Liebigs Ann*., 1995, 1903.
41. a) L. Somogyi, *Carbohydr. Res*., 1977, **54**, C14; b) L. Somogyi, *Carbohydr. Res*., 1978, **64**, 289; c) L. Somogyi, *Carbohydr. Res*., 1987, **165**, 318; d) L. Somogyi, *Carbohydr. Res*., 1988, **182**, 19; e) L. Somogyi, Z. Szabó, and S. Hosztafi, *Liebigs Ann*., 1995, 1393; f) L. Somogyi, M. Czugler, and P. Sohár, *Tetrahedron*, 1992, **48**, 9355.
42. B. Bernet, T. Mäder, and A. Vasella, *Helv. Chim. Acta*, 1997, **80**, 1260.
43. a) E. Bayer and E. Breitmaier, *Tetrahedron Lett*., 1966, 1689; b) E. Bayer and E. Breitmaier, *Chem. Ber*., 1969, **102**, 728; c) J.-D. Charrier, C. Landreau, D. Deniaud, F. Reliquet, A. Reliquet, and J. C. Meslin, *Tetrahedron*, 2001, **57**, 4195; d) R. C. Elderfield and E. C. McClenachan, *J. Am. Chem. Soc*., 1960, **82**, 1982; e) J. L. Corbin and D. E. Work, *Can. J. Chem*., 1974, **52**, 1054; f) G. Trapani, A. Latrofa, A. Reho, and G. Liso, *J. Heterocycl. Chem*., 1989, **26**, 721; g) M. Sako, R. Totani, T. Niwa,

K. Hirota, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, 1990, 915.

44 a) O. Hübner, (H. Lundbeck and Co.) U.S. 2,447,702 (24 Aug 1948) (*Chem. Abstr*., 1948, **42**, 8823); b) K. N. Zelenin, V. A. Alekseev, V. A. Khrustalev, S. I. Yakimovich, V. N. Nikolaev, and N. V. Koshmina, *Zh. Org. Khim*., 1984, **20**, 180 (*Chem. Abstr*., 1984, **100**, 191794c); c) L. Somogyi, *Liebigs Ann*., 1995,721.

45. P. B. Terentyev, V. V. Lashin, V. V. Ovcharenko, G. A. Bulakhov, N. A. Klyuev, M. G. Korotkov, K. N. Zelenin, and O. B. Kuznetsova, *Khim. Geterotsikl. Soedin*., 1993, 1554 (*Chem. Abstr*., 1994, **121**, 300340h).

46. A. M. K. El-Dean, A. A. Atalla, and Sh. M. Radwan, *Afinidad*, 1995, **52**, 115 (*Chem. Abstr*., 1995, **123**, 55200d).

47. a) R.-Y. Yang and L.-X. Dai, *J. Org. Chem*., 1993, **58**, 3381; b) O. Prakash, V. Sharma, H. Batra, N. Rani, P. K. Sharma, and S. P. Singh, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem*., 1998, **37B**, 797; c) X. Huang and Q. Zhu, *J. Chem. Res., Synop*., 2000, 300.

48. a) D. N. Dhar and A. K. Bag, *Indian J. Chem., Sect. B*, 1985, **24B**, 445; b) B. Movassagh, F. Meibodi, and S. Sobhani, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem*., 2002, **41B**, 1296; c) D. Shukla, G.Liu, J. P. Dinnocenzo, and S. Farid, *Can. J. Chem*., 2003, **81**, 744.

49. L. Somogyi, *Liebigs Ann. Chem*., 1985, 1679.

50. C. Neuberg and W. Neimann, *Ber*., 1902, **35**, 2049.

51. M. Freund and C. Meinecke, *Ber.*, 1896, **29**, 2511.

52. a) A. M. Kirkien-Rzeszotarski and W. J. Rzeszotarski, *J. Heterocycl. Chem*., 1977, **14**, 401; b) I. V. Zubets, Yu. A. Boikov, I. V. Viktorovskii, and K. A. V'yunov, *Khim. Geterotsikl. Soedin*., 1986, 1416 (*Chem. Abstr*., 1987, **107**, 7127h).

53. P. P. T. Sah and T. C. Daniels, *Recl. Trav. Chim. Pays-Bas*, 1950, **69**, 1545.

54. W. J. Houlihan and R. E. Manning, (Sandoz Ltd.), Ger. Offen 1,902,449 (1969) (*Chem. Abstr*., 1969, **71**, 123963q).

55. J. Meisenheimer, W. Theilacker, and O. Beißwenger, *Ann.*, 1932, **495**, 249.

56. G. Mazzone, R. Pignatello, A. Panico, S. Mazzone, G. Puglisi, G. Pennisi, G. Raciti, P. Mazzone, and M. Matera, *Pharmazie*, 1992, **47**, 902.

57. D. Libermann, M. Moyeux, A. Rouaix, J. Maillard, L. Hengl, and J. Himbert, *Bull. Soc. Chim. Fr.*, 1953, 957.

58. F. Kurzer and J. L. Secker, *Tetrahedron*, 1981, **37**, 1429.

59. G. Mazzone, G. Puglisi, A. M. Panico, R. Pignatello, A. Corsaro, A. Caruso, M. G. Leone, and M. A. Roxas, *Farmaco Ed. Sci*., 1987, **42**, 963 (*Chem. Abstr*., 1988, **109**, 149434w).

60. A. Gingras, R. W. Hornal, and C. H. Bayley, *Can. J. Chem*., 1960, **38**, 712.

61. S. N. Pandeya, N. Aggarwal, and J. S. Jain, *Pharmazie*, 1999, **54**, 300.
62. H. H. Fox, *J. Org. Chem.*, 1952, **17**, 555.
63. F. E. Anderson, C. J. Duca, and J. V. Scudi, *J. Am. Chem. Soc.*, 1951, **73**, 4967.
64. D. L. Klayman, J. F. Bartosevich, T. S. Griffin, C. J. Mason, and J. P. Scovill, *J. Med. Chem.*, 1979, **22**, 855.
65. P. Pérez-Dubois, P. Souza, J. R. Masaguer, and A. Arquero, *Transition Met. Chem.*, 1987, **12**, 200.
66. H. Taniyama, B. Yasui, H. Aoki, and H. Uchida, *Yakugaku Zasshi*, 1959, **79**, 1462 (*Chem. Abstr.*, 1960, **54**, 6689d).
67. F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 1956, 2853.
68. L. E. Weller, H. M. Sell, and R. Y. Gottshall, *J. Am. Chem. Soc.*, 1954, **76**, 1959.
69. N. Kanoongo, R. V. Singh, and J. P. Tandon, *J. Prakt. Chem.*, 1988, **330**, 479 and 1990, **332**, 815.
70. Guruprasad, R. Patil, and J. S. Biradar, *Asian J. Chem.*, 2000, **12**, 39 (*Chem. Abstr.*, 2000, **132**, 180521w).
71. J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.*, 1951, **73**, 4367.