Transformation of Isatin 3-Acylhydrazones under Acetylating Conditions: Synthesis and Structure Elucidation of 1,5′-Disubstituted 3′-Acetylspiro[oxindole-3,2′-[1,3,4]oxadiazolines]

László Somogyi

Research Group for Antibiotics, Hungarian Academy of Sciences, P.O. Box 70, H-4010 Debrecen, Hungary

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Several substituted isatin 3-acylhydrazones (e.g. **1a–k**, **n**, **p**, **t**) have been synthesized. Under acetylating conditions they were transformed into selectively acetylated derivatives (e.g., **1l**, **n**, **o, q–s**) and into the novel, title spiroheterocycles (**2a–i**). Some side reactions occurring under various acetylating conditions are also discussed.

Isatin (2,3-indolinedione, **3a**) has been known for about 150 years and has recently been found to be, similarly to oxindole (2-indolinone),[1] an endogeneous polyfunctional heterocyclic compound[2] exhibiting biological activity in mammals. A number of hydrazides and aldehyde or ketone acylhydrazones of various acids are known to exhibit metal ion complex-forming properties and/or biological activities. Some 1,3,4-oxadiazoles may also have such properties. In addition, recently we found that 2,2,5-trisubstituted 3-acetyl-1,3,4-oxadiazolines can be physiologically converted by the eucaryote *Alternaria alternata*, used as the model, into ketone acylhydrazone active metabolites.[3] Thus, as an extension of our previous work[4] on the synthesis of spiro[indoline-3,2′-(3′*H*)-[1,3,4]thiadiazoline]-2-ones, we decided an analogous synthesis of the corresponding spiro-oxadiazolines (**2**), a novel type of spiroheterocycles. In order to investigate the scope and limitations of heterocyclization under acylating conditions, various representative types of 3-acylhydrazono-2-indolinones [carbamoyl-, alkanoyl-, and (substituted or hetero)aroyl derivatives] of chemical or potentially biological interest (e.g. **1a–k**, **n**, **p–t**) were synthesized and used as the substrates. We kept in mind, however, that aldehyde and ketone acylhydrazones possess a diminished tendency to cyclize into 1,3,4-oxadiazolines, and an enhanced disposition for the formation of the isomeric diacylhydrazones, due to the lower nucleophilicity of oxygen in comparison to that of sulfur. Thus, a spontaneous thioacylhydrazone $\leftrightarrows$ thiadiazoline equilibrium has been reported e.g. for isatin 3-thioacylhydrazones (**3m**, R = Ph),[5] and an analogous cyclization of isatin 3-thiosemicarbazones (e.g. **3h–l**) has been effected[4] under acetylating conditions (when the heterocyclization preceded the acetylation of the indolinone nitrogen, however, previous presence of the 1-Ac group did not encumber the spirothiadiazoline ring closure). Moreover, with 1,3,4-oxadiazolines, a chance for some undesired transformations must also be considered, e.g. exchange of the endocyclic "acyl moiety" (C-5 of the oxadiazoline ring) by the acylating agent,[6] rearrangement of the oxadiazoline system via a ring-opened azomethine imine intermediate by an exchange between the *exo*- and *endo*cyclic acyl moieties,[7] as well as opening of the oxadiazoline ring (formation of the isomeric diacylhydrazone) eventually accompanied by partial deacylation even under acetylating conditions to result in the formation of monoacylhydrazone.[8]

Results and Discussion

Isatin 3-acylhydrazones may undergo *syn*/*anti* and *E*/*Z* isomerizations.[9] Their literature physical data exhibit discrepancies in some instances. Owing to the more advantageous reaction conditions (enhanced solubility, shorter reaction time, and excellent yields) in this work, the condensation reactions with acid hydrazides were carried out generally in hot acetic acid as the solvent (in some cases also the literature procedures were adopted; however, occasionally the reported data could still not be corroborated: see Table 1 and Chart 1–3).

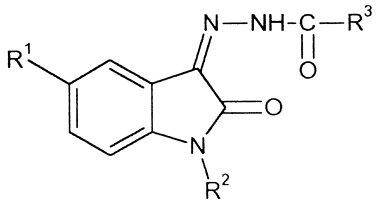
Experiments for the transformation of acylhydrazones **1** were performed at room or elevated temperature using acetic anhydride alone or in the presence of a base (NaOAc, pyridine) or acid (TFA, $ZnCl_2$) additives (see Tables 1 and 2). For cyclization of the acylhydrazones **1** into the spiro compounds **2**, the $Ac_2O/ZnCl_2$ couple, applied previously with good results[10,11] for the cyclization of both aldehyde and ketone acylhydrazones, failed. (With substrates of strong complex-forming properties negative or opposite results—partial deacetylation—have also been observed previously.[8,12]) Thus, when treating the benzoylhydrazones **1c** and **1d** with $Ac_2O/ZnCl_2$ at room temperature for 18 h and at 50 °C for 18 h, respectively, the starting benzoylhydrazones could be isolated almost quantitatively. Reaction of **1c** with hot Ac_2O (72 h at 103 °C) led only to the formation of the 1-acetyl analogue **1m**, thus the presence of an electron-withdrawing group at position 1 is disadvantagious for a subsequent cyclization under such conditions. Even the presence of a strong Broensted acid did not promote cyclization into spirooxadiazoline, or the formation of the isomeric diacylhydrazone. Treatment of the diacetyl compound **1l** with Ac_2O/100% H_2SO_4 at room temperature for up to 7 days and subsequent workup of the reaction mixture with a manifold excess of ice-cold aq NaOAc afforded, with regeneration of the 3-oxo group, 1-acetylisatin (**3d**) and no spiro

Table 1. Preparation and Properties of Acylhydrazones **1a–t** and Acetylisatins **3d**, **e**

Product	Substrate mmol	Agents mmol		Solvent mL	Reaction temp/°C[a] (time/h)	Work-up[b]	Yield/% crude[c] (pure)[c]	Mp/°C (solvent)	Lit. mp (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
1a[d]	**3a**	AH[e]	AcOH	2-PrOH	bp	A	93	239	234–5	$C_{10}H_9N_3O_2$	58.92	4.48	20.63
	10	18	1	10	(4)			(2-PrOH)	(EtOH)[f]	(203.2)	(59.11)	(4.46)	(20.68)
									285 (EtOH)[g]				
1b	**1k**	Ac_2O			bp	C	91	140–1					
	30	636			(3)	D	(64)	(2-PrOH)					
	3g	Ac_2O			bp	B	93	142	143[h]	$C_{11}H_{11}N_3O_2$			
	53	382			(0.75)		(87)	(2-PrOH)	(EtOH)	(217.2)			
1c	**3a**	BH[i]		AcOH	bp	A	94	298–9[j]					
	10	10		15	(3.5)			(AcOH)					
	3a	BH[i]	AcOH	2-PrOH	bp	A	95	300[j]					
	10	10	1.5	40	(3.5)			(2-PrOH)					
	3a	BH[i]	AcOH	EtOH	bp[k]	A	95	306[j]	205	$C_{15}H_{11}N_3O_2$	68.08	4.19	15.75
	10	10	1 drop	50	(2)				(EtOH)[g]	(265.3)	(67.91)	(4.18)	(15.84)
								295	267				
								(EtOH)[l]	(MeOH)[m]				
1d	**3b**	BH[i]		AcOH	bp	E	99	185		$C_{16}H_{13}N_3O_2$	68.77	4.69	14.98
	10	10.1		7.5	(3)[n]		(88)	(2-PrOH)		(279.3)	(68.80)	(4.69)	(15.05)
1e	**3a**	SH[o]		AcOH	bp	A	95	333–4	294[m]	$C_{15}H_{11}N_3O_3$	63.86	3.94	14.84
	10	10.1		15	(4)			(DMF)[p]	(MeOH)	(281.3)	(64.05)	(3.94)	(14.94)
1f	**3b**	SH[o]		AcOH	bp	A	95	250[q]		$C_{16}H_{13}N_3O_3$	65.12	4.39	14.25
	10	10		8	(2)		(88)	(ME/H_2O)[r]		(295.3)	(65.08)	(4.44)	(14.23)
1g	**3a**	IH[s]		AcOH	bp	A	98	303[t]	296[u]	$C_{14}H_{10}N_4O_2$	62.84	3.65	20.87
	10	10		12	(2.3)			(ME/H_2O)[r]		(266.3)	(63.15)	(3.79)	(21.04)
1h	**3b**	IH[s]		AcOH	bp	E	94	219[w]		$C_{15}H_{12}N_4O_2$	64.26	4.33	20.09
	10	10		5	(2)[v]		(70)	(ME/H_2O)[r]		(280.3)	(64.27)	(4.32)	(19.99)
1i	**3c**	SH[o]		AcOH	135	A	98	317		$C_{15}H_{10}BrN_3O_3$	50.12	2.88	11.68
	20	21		25	(2)		(76)	(DMF)[p]		(360.2)	(50.02)	(2.80)	(11.67)
1j	**3a**	SC•HCl[x]	NaOAc	AcOH	bp	F	88	262–3[j]	260[z]	$C_9H_8N_4O_2$			
	10	12	14	5	(1)[y]			(AcOH)	(EtOH)	(204.2)			
1k	**3b**	SC•HCl[x]	NaOAc	AcOH	bp	F	96	224–6[j]	230[bb]	$C_{10}H_{10}N_4O_2$	55.22	4.68	25.59
	10	12	14	6	(1)[y]		(71)	(AcOH)[aa]	(H_2O)	(218.2)	(55.04)	(4.62)	(25.68)
1l	**1j**	Ac_2O			bp	C	90	177	178[h]	$C_{12}H_{11}N_3O_3$			
	5	106			(4.5)	D	(55)	(EtOAc)	(EtOH)	(245.2)			
1m	**1c**	Ac_2O	NaOAc		105	B	99.8[cc]	222[j]					
	2	53	7.3		(0.08)								
	3d	BH[j]		AcOH	103	C	80	224–5		$C_{17}H_{13}N_3O_3$	66.08	4.27	13.62
	10	10		6	(3)	G	(64)	(EtOAc)		(307.3)	(66.44)	(4.26)	(13.68)
1n	**3d**	SH[o]		AcOH[l]	102	A	69	225–7[j]		$C_{17}H_{13}N_3O_4$	63.47	4.13	13.14
	10	10		17	(0.5)		(45)	242–3 (ME)[r]		(323.3)	(63.15)	(4.05)	(13.00)

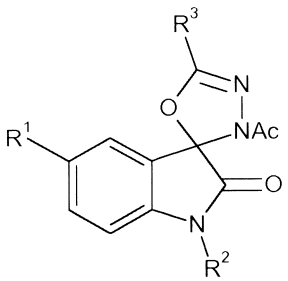
1o	**1e**	Ac_2O	NaOAc		105	B	98[cc)]	162		$C_{19}H_{15}N_3O_5$[ff)]	62.41	4.18	11.45
					(0.33)			(EtOAc)[dd)]		(365.3)	(62.46)	(4.14)	(11.50)
	10	265	36.5					124–5					
								(EtOAc)[ee)]					
	1n	Ac_2O	NaOAc		105	B	99[cc)]	161–2					
	1	32	3.7		(0.33)		(91)	(EtOAc)					
1p	**3e**[gg)]	SH[o),hh)]		AcOH[l)]	102	A	83	214–6[j)]		$C_{17}H_{12}BrN_3O_4$	50.56	3.05	10.35
	10	10		20	(0.5)		(13)[ii)]	253–4		(402.2)	(50.76)	(3.01)	(10.45)
								(ME)[r)]					
1q	**1i**	Ac_2O	TFA[jj)]		73	A[kk)]	49	228[j)]		$C_{17}H_{12}BrN_3O_4$	50.86	2.98	10.27
	15	795	65		(27)		(28)	228		(402.2)	(50.76)	(3.01)	(10.45)
								(66% AcOH)[ll)]					
1r	**1i**	Ac_2O	NaOAc		105	B	99.7	212		$C_{19}H_{14}BrN_3O_5$	51.67	3.12	9.44
	15	398	54.8		(0.33)		(88)	(AcOH)[l)]		(444.2)	(51.37)	(3.18)	(9.46)
	1q	Ac_2O	NaOAc		100	B	95.7[cc)]	210–1[j)]					
	1	32	3.65		(0.33)								
1s	**1f**	Ac_2O	NaOAc		105	B	96[cc)]	169		$C_{18}H_{15}N_3O_4$	64.13	4.48	12.64
	10	265	36.5		(0.33)		(85)	(EtOAc/hexane)		(337.3)	(64.09)	(4.48)	(12.46)
1t	**1g**	Ac_2O	NaOAc		101	B	96	178–9[j)]					
	1	26	3.65		(0.1)								
	3d	IH[s)]		AcOH[l)]	102	A[mm)]	(36.5)	180		$C_{16}H_{12}N_4O_3$	62.63	4.00	18.22
	10	10		10	(3)			(EtOAc)		(308.3)	(62.33)	(3.92)	(18.17)
3d	**3a**	Ac_2O	NaOAc		102	B	91	142–3[j)]	141–2[j),nn),oo)]				
	10	44.5	3		(0.05)				142–3.5				
									(PhH)[oo)]				
3e	**3c**•H_2O	Ac_2O	NaOAc		102	B	~100	168	170–2				
	30	134	9		(0.05)		(68)[c)]	($CHCl_3$/EtOAc)	(PhH)[pp)]				
									166				
									(AcOH)[qq)]				

a)Bath if not bp. b) For general operations of processing the reaction mixtures see Experimental. c) Without workup of the mother liqors. d) Compound **1a** was obtained also by treating hydrazone **3f** (8 mmol) with hot Ac_2O (69 mmol) for 1 h. Extraction of the crude product with $CHCl_3$, to remove diacetyl compound **1l**, and subsequent recrystallization of the undissolved solid from 2-PrOH afforded pure **1a**. e) Acetohydrazide. f) Ref. 17b. g) Ref. 17c. h) Ref. 17a. i) Benzohydrazide. j) Crude product. k) Synthesis executed according to ref. 17c. l) 99–100%. m) Ref. 22. n) When the reaction was completed, water (5mL) was added to the hot reaction mixture. o) Salicylohydrazide. p) With adding a bit of water to the hot solution. q) For the crude product, mp 252–253 °C. r) ME = 2-methoxyethanol; ME/H_2O = with addition of water to the hot solution. s) Isonicotinohydrazide (isoniazid). t) For the crude product, mp 305 °C. u) Ref. 23. v) When completed, water (13 mL) was added to the hot reaction mixture. w) For the crude product mp 215 °C. x) Semicarbazide hydrochloride. y) When completed, water (15 mL) was added in the cold. z) Ref. 16a; Ref. 16b 260 °C (H_2O); Ref. 9b *syn* isomer, 260 °C (BuOH) and *anti* isomer, 258.5 °C (EtOH). aa) When recrystallized from DMSO with addition of water, mp 220–221 °C. bb) Ref. 16b; Ref. 9b *syn* isomer 224 °C (40% EtOH) and *anti* isomer 229.5 °C, respectively. cc) TLC homogeneous. dd) Needles. ee) Blocks. ff) On the basis of ^{1}H NMR spectra both modifications contain 0.75 H_2O. gg) Mp 168 °C. hh) Mp 149–150 °C. ii) In the course of recrystallization the product decomposed partially, thus Ac_2O/NaOAc acetylation of the material dissolved in the recrystallization mother liquor and subsequent column chromatography afforded 2-acetoxy-*N*,*N*′,*N*′-triacetyl-benzohydrazide (**4c**, the synthesis of an *N*,*O*-diacetyl derivative **4b** has been reported previously[25]). jj) Trifluoroacetic acid ≥ 98%, Fluka. kk) Workup of the mother liquor of the crude product yielded spirocompound **2i**. ll) Mp 233 °C (from $CHCl_3$). mm) On cooling deacetylation product **1g** (25%, mp 304 °C) separated. Removal of the solvent of the mother liquor and subsequent purification of the residue by column chromatography [silica gel 60; solvent, $CHCl_3$/EtOAc (8:2)] afforded **1t**. nn) Mp corrected. oo) Ref. 14. pp) Ref. 24. qq) Ref. 15.



	R^1	R^2	R^3
1a	H	H	Me
b	H	Me	Me
c	H	H	Ph
d	H	Me	Ph
e	H	H	C_6H_4(OH)-(2)
f	H	Me	C_6H_4(OH)-(2)
g	H	H	C_5H_4N-(4)
h	H	Me	C_5H_4N-(4)
i	Br	H	C_6H_4(OH)-(2)
j	H	H	NH_2
k	H	Me	NH_2
l	H	Ac	Me
m	H	Ac	Ph
n	H	Ac	C_6H_4(OH)-(2)
o	H	Ac	C_6H_4(OAc)-(2)
p	Br	Ac	C_6H_4(OH)-(2)
q	Br	H	C_6H_4(OAc)-(2)
r	Br	Ac	C_6H_4(OAc)-(2)
s	H	Me	C_6H_4(OAc)-(2)
t	H	Ac	C_5H_4N-(4)

Chart 1.

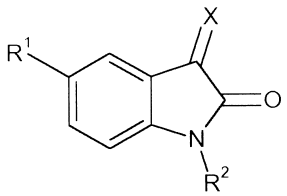


	R^1	R^2	R^3
2a	H	Ac	Me
b	H	Me	Me
c	H	Ac	Ph
d	H	Me	Ph
e	H	Ac	C_6H_4(OAc)-(2)
f	H	Me	C_6H_4(OAc)-(2)
g	H	Ac	C_5H_4N-(4)
h	H	Me	C_5H_4N-(4)
i	Br	Ac	C_6H_4(OAc)-(2)

Chart 2.

compound was produced. Eventually, for acid-catalyzed cyclizations, treatment of some 3-acylhydrazono-oxindoles and selectively acetylated derivatives with Ac_2O/TFA proved to be convenient (see Table 2).

Previously the Ac_2O/pyridine as well as the Ac_2O/NaOAc



	R^1	R^2	X
3a	H	H	O
b	H	Me	O
c	Br	H	O
d	H	Ac	O
e	Br	Ac	O
f	H	H	NNH_2
g	H	Me	NNH_2
h	H	H	$NNH(CS)NH_2$
i	H	Me	$NNH(CS)NH_2$
j	H	Ac	$NNH(CS)NH_2$
k	H	H	NNH(CS)NHPh
l	H	Me	NNH(CS)NHPh
m	H	H	NNH(CS)R

Chart 3.

couples were found to be useful for cyclization of aldehyde acylhydrazones (especially aroylhydrazones) into the corresponding 3-acetyl-1,3,4-oxadiazolines. Unexpectedly, when isonicotinoylhydrazone (**1g**) was boiled with Ac_2O/py (5:1) for 7.5 h, transacetylated products acetylhydrazone **1l**, and the 5′-methyl spiro compound **2a** formed (and isonicotinic acid could be isolated in 80% yield) instead of the anticipated 5′-(4-pyridyl)oxadiazoline **2g**. Acetylation of isonicotinohydrazide (isoniazid) and subsequent easy deacylation to give hepatotoxic acetohydrazide under physiological conditions have been comprehensively investigated even in the last decade[13] with regard to the therapeutic and adverse effects. Eventually, the synthesis of the pyridyl derivative **2g** could be effected in high yield by treating **1g** with hot Ac_2O alone (see Table 2).

In an attempted synthesis of the spiro compound **2c** or the isomeric diacylhydrazone, treatment of the benzoylhydrazone **1c** with the Ac_2O/NaOAc couple at 105 °C afforded the 1-acethyl derivative **1m** almost quantitatively in 5 min; thus only the cyclic amide moiety underwent a selective transformation and no diacylhydrazone nor any transacylated product was formed. The same substance (**1m**) was obtained in good yield by condensing 1-acetylisatin (**3d**) with benzohydrazide in AcOH, as well. (However, when condensing **3d** with isonicotinohydrazine, in a parallel reaction under the same reaction conditions, partial deacetylation took place, and besides the target compound, **1t**, a considerable amount of **1g** could be isolated.) Similarly, selective acetylation of **1g** with Ac_2O/NaOAc afforded pure **1t** in an excellent yield (see Table 1). The prompt acetylation of the cyclic amide nitrogen in this way is remarkable, since for acetylation of the isatins **3a** and **3c** boiling with Ac_2O for 4 h[14] and 1–2 h,[15] respectively, has been reported. With the Ac_2O/NaOAc coupole also, acetylation of isatins **3a**, **c** was observed in 3 min (see Table 1). As treatment with Ac_2O/NaOAc transformed the salicyloylhydrazones **1e**, **f**, **i**, **n** into 2-acetoxybenzoylhydrazone derivatives

Table 2. Preparation and Properties of Spiro-oxindoles **2a–i**

Product	Substrate mmol	Agents mmol		Reaction temp/°C[a] (time/h)	Work-up[b]	Yield/% crude[c] (pure)[c]	Mp/°C (solvent)	Formula (mol. mass)	Analysis found (calcd) C	H	N
2a	**1l**	Ac_2O	NaOAc	150	C	24	159	$C_{14}H_{13}N_3O_4$	58.83	4.64	14.70
	25	636	76.8	(6)	G[d]	(13.5)	($CHCl_3$/hexane)	(287.3)	(58.53)	(4.56)	(14.63)
2b	**1b**	Ac_2O	NaOAc	150	C		186	$C_{13}H_{13}N_3O_3$	60.32	5.09	16.21
	15	583	86	(8)	G[e]	(44)	(EtOAc)	(259.3)	(60.22)	(5.05)	(16.21)
2c	**1c**	Ac_2O	TFA[f]	75	C	35	146	$C_{19}H_{15}N_3O_4$	65.49	4.30	12.07
	50	1060	130	(46)	D[g]	(16.5)	(EtOAc/hexane)	(349.3)	(65.32)	(4.33)	(12.03)
2d	**1d**	Ac_2O	TFA[f]	70	C		172	$C_{18}H_{15}N_3O_3$	67.53	4.80	13.12
	10	212	26	(42)	H[h]	(52)	(Et_2O/hexane)	(321.3)	(67.28)	(4.71)	(13.08)
	1d	Ac_2O	py[i]	140	C	(40)	172				
	10	212	26	(3)	H[h]		(Et_2O/hexane)				
2e	**1e**	Ac_2O	TFA[f]	75	C	68	224	$C_{21}H_{17}N_3O_6$	61.52	4.28	10.30
	30	636	78	(36)	D[j]	(58)	($CHCl_3$/2-PrOH)	(407.4)	(61.91)	(4.21)	(10.32)
	1n	Ac_2O	py[i]	r.t.[k]	C	87[l]					
	0.5	21	19	(68)	G						
	1o	Ac_2O	py[i]	r.t.[k]	C	79[l]					
	0.5	21	19	(62)	G						
	1o	Ac_2O	TFA[f]	73	C	92[m]	220–2[n]				
	0.5	21	2.6	(21)	D						
2f	**1f**	Ac_2O	TFA[f]	70	C	67	177	$C_{20}H_{17}N_3O_5$	63.23	4.49	11.09
	15	318	39	(16)	D	(61)	(PhH/hexane)	(379.4)	(63.32)	(4.52)	(11.08)
	1s	Ac_2O	TFA[f]	73	C	43	175–6[n]				
	1	42	5.2	(18)	D						
2g	**1g**	Ac_2O		103	C	96	175	$C_{18}H_{14}N_4O_4$	61.97	4.05	16.05
	10	530		(29)	G	(73)	(EtOAc/hexane)	(350.3)	(61.71)	(4.03)	(15.99)
2h	**1h**	Ac_2O	TFA[f]	75	C	80	201	$C_{17}H_{14}N_4O_3$	63.45	4.40	17.35
	10	212	26	(46)	D[o]	(60)	(EtOAc)	(323.3)	(63.35)	(4.38)	(17.38)
2i	**1i**	Ac_2O	TFA[f]	72	A,[p]I	45.5	221	$C_{21}H_{16}BrN_3O_6$	51.89	3.26	8.56
	15	795	65	(28)	J,K	(38)	($CHCl_3$/EtOAc)	(486.3)	(51.87)	(3.32)	(8.64)
	1r	Ac_2O	TFA[f]	72	C	92	221–2				
	5	212	26	(48)	J	(87)	($CHCl_3$/EtOAc)				

a) Bath. b) See general operations of processing the reaction mixtures, Experimental. c) Without workup of the mother liquors of crystallization. d) The dry solid so obtained was crystallized from EtOAc to give 37% unreacted **1l**. The material dissolved in the mother liquor was separated by column chromatography [Silica Woelm 100–200 µm; solvent, $CHCl_3$/EtOAc (95:5)] to give pure **2a**. e) Purification by column chromatography [Silica Woelm 100–200 µm; solvent, $CHCl_3$/EtOAc (95:5)] afforded pure **2b** and 51.5% unreacted **1b**. f) Trifluoroacetic acid ≥ 98%, Fluka. g) The dry solid so obtained was crystallized from EtOAc to give 4% 1-acetyl derivative **1m**. Column chromatography of the material dissolved in the mother liquor [Silica Woelm 100–200 µm; solvent, $CHCl_3$/EtOAc (95:5)] afforded pure **2c**, and 0.9% transacylated hydrazone **1l**. h) Column chromatography [solvent, $CHCl_3$/Et_2O (95:5)] afforded pure **2d** and ~3% unreacted **1d**. i) Anhydrous pyridine. j) Column chromatography [silica gel; solvent, $CHCl_3$/EtOAc (95:5)] afforded pure product. k) Room temperature. l) It contains compound **1o** as minor component [TLC, $CHCl_3$/EtOAc (95:5)]. m) TLC [$CHCl_3$/EtOAc (95:5)] practically homogeneous. n) Crude product. o) A solution of the solid residue in $CHCl_3$ was washed with aq $NaHCO_3$ and water, dried ($MgSO_4$), treated with charcoal and then concentrated. The residue was crystallized from Et_2O with addition of hexane to give crude product. p) The solid was **1q** (yield 48.6%).

(**1o**, **r**, **s**), 1-acetylisatin salicyloylhydrazones (**1n**, **p**) were synthesized by condensing 1-acetylisatins (**3d**, **e**) with salicylohydrazide (**4a**). The reaction of the salicyloylhydrazone **1i** with Ac_2O/TFA at 73 °C for 27 h gave the acetylsalicyloylhydrazone **1q** (a structural isomer of the 1-acetyl derivative **1p**, see Table 1). As to the sensitivity of the salicyloylhydrazone **1p** towards solvolysis, as well as the preparation of a tetraacetyl derivative (**4c**) of **4a** see footnote ii and Experimental. Because of the occasional poor solubility of the substrates under the admissible reaction conditions for preparing the spiro-oxadiazolines **2**, transformation of the preacetylated intermediates seems to be more expedient [e.g. transformations **1o** → **2e** and **1r** → **2i**, Table 2].

Semicarbazones are known to undergo degradation into acetylhydrazones[8] under acetylating conditions. Thus, for the preparation of the acetylhydrazones **1b**, **l** first the easily accessible[9b,16] semicarbazones **1j**, **k** (see Table 1) were treated with hot acetic anhydride; nevertheless, acetylation of the more versatile synthone hydrazones (**3f**, **g**)[17] by known methods was proved to give products with higher purity.

For the structure elucidation of the acetylated acylhydrazones (**1**) and spiro[oxindoleoxadiazolines] (**2**) the IR spectra (see Tables 3 and 5) did not offer sufficient essential information because the carbonyl vibrations of the cyclic and *exo*cyclic amides, diacyl amines and ester moieties together could not be unambigously examined.

Table 3. Characteristic IR Carbonyl Bands of Acylhydrazones **1** and Oxindoles **3**

Compound	$\nu_{C=O}$ (KBr)/cm^{-1} a)
1a	1698, 1666, 1654
1b	1706 (m), 1688, 1674 (m)
1c	1700, 1692, 1684
1d	1698, 1680
1e	1712, 1694, 1662
1f	1700, 1674
1g	1722, 1694, 1674
1h	1700, 1682
1i	1710, 1698
1j	1704[b]
1k	1732, 1682[c]
1l	1704, 1682
1m	1712, 1698
1n	1712, 1654
1o[d]	1768, 1719, 1698
1p	1728, 1714, 1646
1q	1764, 1706, 1680
1r	1774, 1720, 1696
1s	1770, 1698, 1684
1t	1706
3a	1748, 1728[e]
3b	1742, 1730
3d	1782, 1746, 1716[f]
3e	1786, 1770, 1746, 1710[g]
3f	1688
3g	1686, 1676

a) The bands are strong if not otherwise indicated. b) Ref. 9b: for solution in DMSO, 1716, 1695 (*syn*), and 1725 (*anti*) c) Ref. 9b: for solution in DMSO, 1713, 1688 (*syn*). d) The needles modification, mp 162 °C. e) Ref. 15: 1755, 1740 ($CHCl_3$). f) Ref. 15: 1775, 1742, 1721 ($CHCl_3$). g) Ref. 15: 1786, 1745, 1725 ($CHCl_3$).

The presence and number of various groups (NH, OH, NMe, NAc, OAc) could be stated on the basis of the ^{1}H NMR data. Signals 7-H and 1-C(O)CH_3 are significantly downfield shifted for the 1-Ac derivatives (see Table 4 and 5). The obtained spiro[oxindoleoxadiazolines] **2** are colorless compounds indicating the lack of conjugation at C-3 which exists in **1** and **3**. The ^{13}C NMR signal of compounds **2** at δ 91–93 unequivocally reveals the spiro-1,3,4-oxadiazoline structure, and that of C-5′ [O–*C*(R^3)=N–N] at δ 152–155 (see Table 5), which is regularly downfield shifted as compared to the C-3 (*C*=N–NH–) signal of the 3-hydrazono-2-indolinones **1b**, **o**, **s** and **3g** resonating at δ 140–148 (see footnotes of Table 4). The upfield-shifted 5′-Me signals at δ 11.2 in the spectrum of **2a**, **b** (see Table 5) serve[7,11,12] as additional evidence for the oxadiazoline structure.

The ^{1}H NMR spectrum of the acylhydrazone **1o** (both modi-

Table 4. Characteristic ^{1}H NMR Spectral Data of Acylhydrazones **1** and Oxindoles **3**[a]

Compound	NH/OH	δ/ppm[b] 7-H[c]	NCH_3[d]	$C(O)CH_3$[d]
1a	[e]12.50, 11.22			2.32
1b	[f]13.11,[g] 12.51[h]	6.89	3.27	2.44,[i] 2.24[j]
1l	[f]12.26	8.26		2.72,[k] 2.46
1m	[f]13.65	8.27		2.78[k]
1n	[f]14.31, 11.98	8.18		2.64[k]
1o[l]	[e]13.29	8.18		2.63,[k] 2.35
1p	[e]14.31, 12.03	8.12		2.63[k]
1q	[e]13.57,[m] 11.47[n]	6.93		2.30,[o] 1.91[p]
1r	[e]13.23	8.12		2.62,[k] 2.34
1s	[f]13.77	6.89	3.29	2.39
1t	[f]13.79	8.28		2.78[k]
3b	[f]	6.90	3.26	
3d	[f]	8.43		2.75[k]

a) For ^{13}C NMR data of compounds **1b**, **o**, **s**, and **3g** see the footnotes here below. b) For solutions in $CDCl_3$ or $[CD_3]_2SO$ as indicated before the columns. c) Doublet shaped m, centered at. d) 3 H, s. e) For solutions in $[CD_3]_2SO$. f) For solutions in $CDCl_3$. g) 0.25 H. h) 0.75 H. i) 2.25 H, 0.75 Ac. j) 0.75 H, 0.25 Ac. k) 1-Ac. l) The needles modification, mp 162 °C. For solution of the blocks modification, ^{1}H NMR ($CDCl_3$): δ 13.47 (bs, ~1 H, NH), 8.26 (mc, 1 H, 7-H), 2.74 (s, 3H, 1-Ac), 2.39 (s, 3 H, OAc). m) 0.91 H, and at δ 14.38 (0.09 H). n) 1 H, s, 1-H. o) 2.78 H, s, 0.93 Ac. p) 0.22 H, s, 0.07 Ac. ^{13}C NMR ($[CD_3]_2SO$) data: **1b** δ 172.59 (CH_3–*C*=O), 160.46 (*endo*cyclic *C*=O), 143.37 (*C*=NNH), 25.55 (*C*H$_3$–N), 19.07 (*C*H$_3$–C=O); **1o** (the needles modification, mp 162 °C) δ 170.02 and 169.08 (*C*=O), 161.34 (*endo*cyclic *C*=O), 148.15 (*C*=NNH), 26.34 and 21.06 (*C*H$_3$–C=O), the spectrum is identical with that of the blocks modification (mp 123–125 °C); **1s** δ 168.98 (*C*=O), 160.72 (*endo*cyclic *C*=O), 148.19 (*C*=NNH), 25.65 (*C*H$_3$–N), 20.88 (*C*H$_3$–C=O); **3g** δ 160.80 (*endo*cyclic *C*=O), 139.95 (*C*=NNH), 25.04 (*C*H$_3$–N). For ^{13}C NMR spectral data of isatin and some (3-substituted)oxindoles see Ref. 26.

Table 5. Characteristic IR-, ^{1}H-, and ^{13}C NMR Spectral Data of Spiroindolinones **2a–i**

Compound	IR (KBr)[a] $\nu_{C=O}$/cm^{-1}	NMR ($CDCl_3$) δ/ppm					
		^{1}H		^{13}C			
		7-H[b]	CH_3[c]	C=O	C-5′	C-3,2′	CH_3[d]
2a	1742	8.30	2.69[e]	170.06[g]	155.36	92.46	26.29[e]
	1670		2.25[f]	166.98			20.94
			2.19[h]				11.20[i]
b	1750		3.23[j]	168.89	155.41	92.51	26.41[j]
	1740		2.23[j]	166.34			21.09
	1654		2.15[h]				11.22[i]
c	1780	8.34	2.70[e]	170.10	155.03	92.80	26.36[e]
	1722		2.36[f]	169.94			21.04
	1674			167.26			
	1662						
d	1742		3.29[j]	168.83	155.11	92.96	26.49[j]
	1662		2.36[f]	166.72			21.20
e	1782	8.33	2.70[e]	170.07	152.17	92.01	26.31[e]
	1718		2.34[f]	169.78			21.11
	1664		2.29[k]	168.96			20.94
				166.95			
f	1772		3.28[j]	169.02	152.24	92.10	26.49[j]
	1736		2.33[f]	168.62			21.21
	1676		2.29[k]	166.43			20.88
g	1782	8.35	2.70[e]	169.94	153.08	93.45	26.31[e]
	1712		2.38[f]	169.58			21.03
	1676			167.46			
h	1784		3.29[j]	168.47	153.19	93.57	26.56[j]
	1722		2.37[f]	166.98			21.22
	1672						
i	1774	8.25	2.69[e]	169.93	152.09	91.21	26.32[e]
	1720		2.35[l]	169.12			21.12
	1672		2.34[l]	168.95			20.99
				167.09			

a) All the bands are strong. b) m centered at, 1 H. c) s, 3 H. d) That of Ac if not otherwise indicated. e) 1-Ac. f) 3′-Ac. g) 2C. h) Presumably the signal of 5′-Me. i) 5′-Me. j) 1-Me. k) OAc. l) NAc and/or OAc.

fications, see Table 1 and 4) exhibits a sharp unexpected signals (s, ~1.5 H, scarcely exchangeable by treatment with D_2O even for 4 days), of the blocks modification at δ 2.17 ($CDCl_3$) and of the more thermostable needles at δ 2.09 ($[CD_3]_2SO$]. X-ray diffraction analysis of the more suitable blocks modification revealed the presence of water of crystallization hydrogen-bonded to the 1-Ac, *endo*- and *exo*cyclic amide moieties of neighboring **1o** molecules (see Fig. 1); thus, the alternative to a covalent hydration can be excluded. A similar finding has been reported[18] for 4-hydroxybenzaldehyde nicotinoylhydrazone monohydrate.

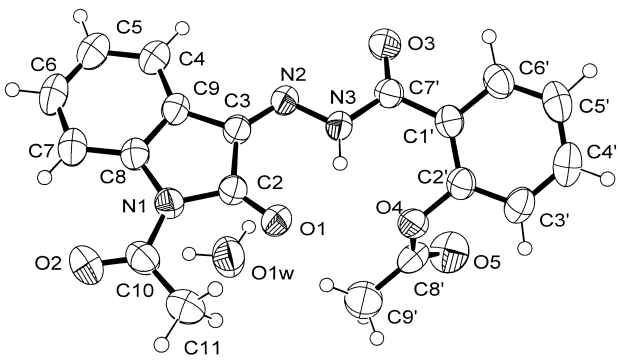


Fig. 1. ORTEP drawing of compound **1o** with 50% of the thermal ellipsoids.

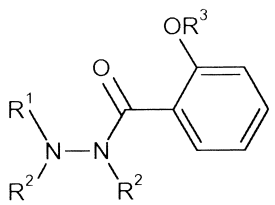
Experimental

Melting points (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (< 50 °C, bath temperature). TLC: Kieselgel 60 F_{254} (Merck, Alurolle). IR (KBr discs): Perkin-Elmer 16 PC-FT spectrometer. 200 MHz ^{1}H and 50 MHz ^{13}C NMR spectroscopy (the latter by *J*-echo techniques) for $CDCl_3$ and $[CD_3]_2SO$ solutions with TMS as the internal standard and deuterium signal of the solvent as the lock: Bruker WP 200 SY spectrometer. X-ray diffraction analysis [for yellow block crystals (0.75×0.65×0.6 mm) of **1o** ($C_{19}H_{17}N_3O_6$) grown from EtOAc, M = 383.36, orthorhombic, a = 11.051(2) Å, b = 13.368(3) Å, c = 24.389(3) Å, V = 3603(1) Å^3, Z = 8, space group: Pbca, ρ_{calc} = 1.413 g cm^{-3}]. Enraf Nonius MACH3 diffractometer, data were collected at 293(1) K, Mo $K\alpha$ radiation λ = 0.71073 Å ω-2θ motion, θ_{max} = 25.3°, 3231 reflections of which 2438 were unique with $I > 2\sigma(I)$, decay: 2%. The structure was solved using the SIR-92 software[19] and refined on F^2 using the SHELXL-97[20] program; the publication material was prepared with the WINGX-97 suite,[21] R(F) = 0.047 and $wR(F^2)$ = 0.163 for 3231 reflections, 305 parameters. The complete data for the

three crystals are deposited as Document No. 74034 at the Office of the Editor of Bull. Chem. Soc. Jpn. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers CCDC 157190.

General Operations of Processing the Reaction Mixtures. (see Tables 1 and 2). (A) The product was filtered off in the cold. (B) The reaction mixture was cooled and 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 h; then hexane was added. (E) Water was added to the hot reaction mixture. (F) The mixture was cooled and water was added. (G) The cold residue was triturated with water. (H) The cold residue was triturated with EtOH, kept at room temperature for ~0.5 h and then concentrated and triturated with Et_2O; to the crystalline material hexane was added. (I) The filtrate was concentrated. (J) Trituration of the cold residue with 2-PrOH and subsequent addition of hexane afforded a crude product. (K) A solution of the product in $CHCl_3$ was treated with charcoal and then concentrated. The residue was crystallized from the solvent indicated in the Table.

2-Acetoxy-N,N′,N′-triacetyl-benzohydrazide (4c). A mixture of the salicylohydrazide **4a** (1.5215 g, 10 mmol), anhydrous NaOAc (1.500 g, ~18.3 mmol), and Ac_2O (15 ml, 159 mmol) was stirred at 103 °C (bath) until dissolution was complete (~10 min) and for an additional 30 min, and then concentrated. The residue was treated with ice/water and extracted with $CHCl_3$, the organic layer was washed with aq $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Purification of the residue by column chromatography [silica gel 60, $CHCl_3$/EtOAc (98:2)] afforded the pure product (**4c**, 1.730 g, 54%), mp 65 °C (from EtOAc with additon of hexane) (Chart 4) 360 MHz ^{1}H NMR ($CDCl_3$): δ 7.58–7.52 (m, 2H) and 7.32–7.22 (m, 2H) (4 aromatic H), 2.38 (s, 6H), 2.35 (s, 3H), and 2.29 (s, 3H) (all the 3 signals are split by 1.4 Hz, presumably due to a hindered rotation, 4 Ac). IR (KBr) 1746 (s), 1736 (s), 1714 (s), 1688 (s), 1606 cm^{-1} (m). Found: C, 56.32; H, 4.95; N, 8.75%. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.24; H, 5.04; N, 8.75%.



	R^1	R^2	R^3
4a	H	H	H
b	Ac	H	Ac
c	Ac	Ac	Ac

Chart 4.

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