Synthesis of Isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones and 4-Acyl-5-hydroxy-3(2*H*)-pyridazinones

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The title compounds were prepared from ethyl 5-acyl- or 5-(1-hydroxyethenyl)isoxazole-4-carboxylates which in turn were prepared from ethyl 3-methylamino-2-butenoate or 3(2*H*)-furanones.

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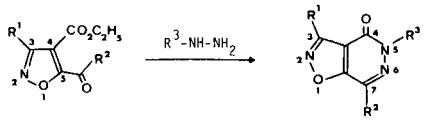
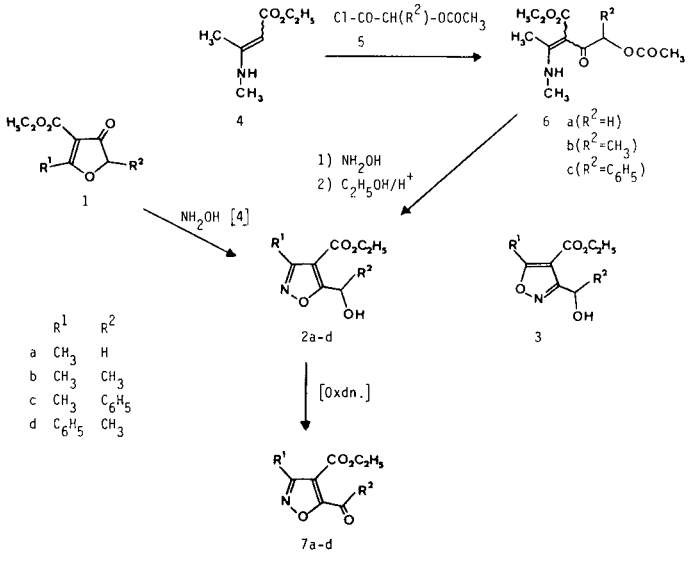
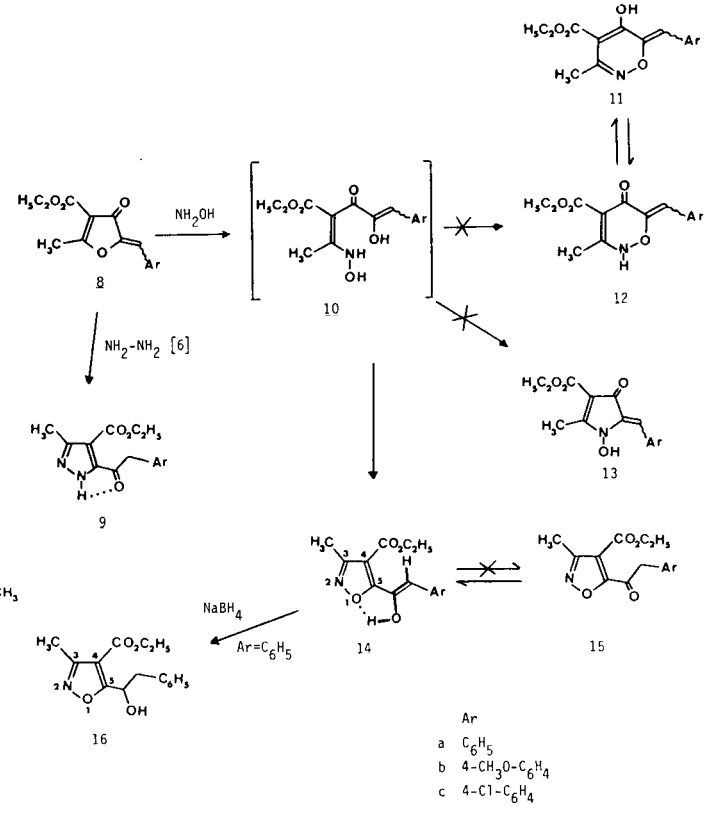
Only a few derivatives of the isoxazolo[4,5-*d*]pyridazin-4(5*H*)-one system are known. The reported compounds were prepared from diethyl 3-phenylisoxazole-4,5-dicarboxylate [1,2] or ethyl 5-cyano-3-methylisoxazole-4-carboxylate [3]. Consequently the substituent at C-7 of the ring system is a hydroxy group or a group resulting from its transformation (methoxy, chloro or bromo). The formation of 7-alkyl-or 7-phenylisoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones could be expected from the reaction of hydrazines with ethyl 5-acyl-or 5-benzoylisoxazole-4-carboxylates:



Scheme A



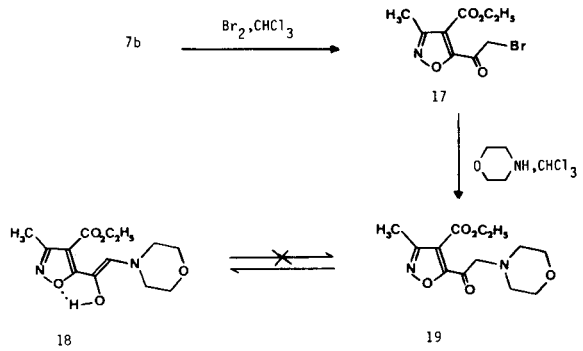
Scheme B



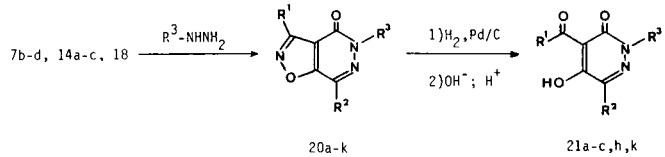
In this report we describe an access to these precursors, starting from ethyl 3-methylamino-2-butenoate or 3(2*H*)-furanones, which allows the introduction of a methyl, phenyl, arylmethyl or aminomethyl group at C-7 of the isoxazolo[4,5-*d*]pyridazin-4(5*H*)-one system. Some of the isoxazolopyridazinones obtained were converted to the corresponding 4-acyl-5-hydroxy-3(2*H*)-pyridazinones by a classical hydrogenolysis-hydrolysis sequence. Although a large volume of work has appeared on 3(2*H*)-pyridazinones due to their interesting biological properties, we found no example of 4-acyl-5-hydroxy derivatives.

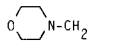
A few years ago, we reported on the synthesis of ethyl 5-(1-hydroxyalkyl)isoxazole-4-carboxylates **2a,b,d** by reaction of 3(2*H*)-furanones **1** with hydroxylamine [4] (Scheme A). This reaction proceeds with a good to complete regiospecificity since only 5% of the isomeric isoxazole **3** was detected when R^2 = H. In this report we have explored an

Scheme C



Scheme D



	R^1	R^2	R^3		R^1	R^2	R^3
a	CH_3	CH_3	H	g	CH_3	C_6H_5	$C_6H_5CH_2$
b	CH_3	C_6H_5	H	h	CH_3	$C_6H_5CH_2$	H
c	C_6H_5	CH_3	H	i	CH_3	4-CH_3O-C_6H_4-CH_2	H
d	CH_3	CH_3	C_6H_5	j	CH_3	4-Cl-C_6H_4-CH_2	H
e	CH_3	C_6H_5	C_6H_5	k	CH_3		H
f	CH_3	CH_3	$C_6H_5CH_2$				

alternate more simple synthetic route which allows to prepare compounds **2a-c** from ethyl 3-methylamino-2-butenoate (**4**) with a fair yield and without intermediate purification. Reaction of hydroxylamine with the crude ethyl 2-acyl-3-methylamino-2-butenoates **6** prepared by the Benary's method [5] and subsequent acidic ethanolysis yielded regiospecifically the alcohols **2a-c**. An attempt to synthetize compound **2d** in a similar manner, starting from ethyl 3-methylamino-3-phenylpropenoate, failed. Oxidation of compounds **2**, either by means of pyridinium chlorochromate (**2a**) or by Jones' method, **2b-d**, afforded the 5-formyl, 5-acetyl- or 5-benzoylisoxazoles **7a-d**. The structures of compounds **7** were consistent with the microanalytical and spectral data (Tables 1 and 2).

The appropriate precursors for the introduction of an arylmethyl group at C-7 of the isoxazolo[4,5-*d*]pyridazin-(4,5*H*)-one system seemed to be ethyl 5-arylacetyl-3-methylisoxazole-4-carboxylates (**15**). In 1977 we have described the synthesis of ethyl 3-arylacetyl-5-methylpyrazole-4-carboxylates (**9**) by action of hydrazine on 2-arylidene-3(2*H*)-furanones **8** [6] (Scheme B). When compound **8a** was reacted with hydroxylamine, one single yellow compound was formed. Surprisingly no resonance appeared for a benzylic methylene in the ^{1}H-nmr spectrum and consequently the structure **15** was immediately ruled out. The 300 MHz ^{1}H-nmr spectrum of the product displayed a doublet at δ 6.48 for one ethylenic proton, one doublet at δ 7.84 and two triplets at δ 7.23 and 7.35 for the phenyl group and a doublet at δ 11.01 for one exchangeable proton. Irradiation at δ 11.01 transformed the resonance at δ 6.48 into a singlet and proved that the ethylenic proton and the ex-

Table 1

Physical Data for Compounds **7**, **14**, **18**

Compound No.	Yield (%)	Bp (°C)/torr Mp (°C) (solvent)	Molecular Formula	Analyses % Calcd./Found C	H	N	IR(cm^{-1}) (Chloroform)	UV (Ethanol) λmax (ε max)
7a	60 [a]	99-104/1	$C_8H_9NO_4$	52.46 52.44	4.95 5.03	7.65 7.72	1730, 1705, 1605	219 (7500)
7b	86 [a]	116/1.5	$C_9H_{11}NO_4$	54.82 54.55	5.62 5.59	7.10 7.19	1725, 1600	240 (6100)
7c	90 [a]	62 ethanol	$C_{14}H_{13}NO_4$	64.86 64.82	5.05 4.96	5.40 5.35	1725, 1675, 1600	261 (14600)
7d	57 [a]	175-178/2	$C_{14}H_{13}NO_4$	64.86 64.60	5.05 5.07	5.40 5.40	1740, 1710, 1610	233 (17300)
14a	85 [b]	130 ethanol	$C_{15}H_{15}NO_4$	65.92 65.73	5.53 5.60	5.13 4.98	3100, 2780, 1675, 1640(weak), 1565	350 (20300)
14b	76 [b]	142 ethanol	$C_{16}H_{17}NO_5$	63.36 63.42	5.65 5.59	4.62 4.70	3100, 2780, 1680, 1640(weak), 1565	369 (29300)
14c	66 [b]	152 ethanol	$C_{15}H_{14}NO_4Cl$ [d]	58.55 58.80	4.59 4.56	4.55 4.47	3100, 2780, 1680, 1640(weak), 1570	351 (26200)
18	51 [c]	120 ethanol	$C_{13}H_{18}N_2O_5$	55.31 55.11	6.43 6.51	9.92 9.88	3100, 2840, 1680, 1640(weak), 1560	388 (15400)

[a] From compounds **2**. [b] From compounds **8**. [c] From compound **7b**. [d] Cl analysis %, Calcd./Found: 11.52/11.42.

Scheme F

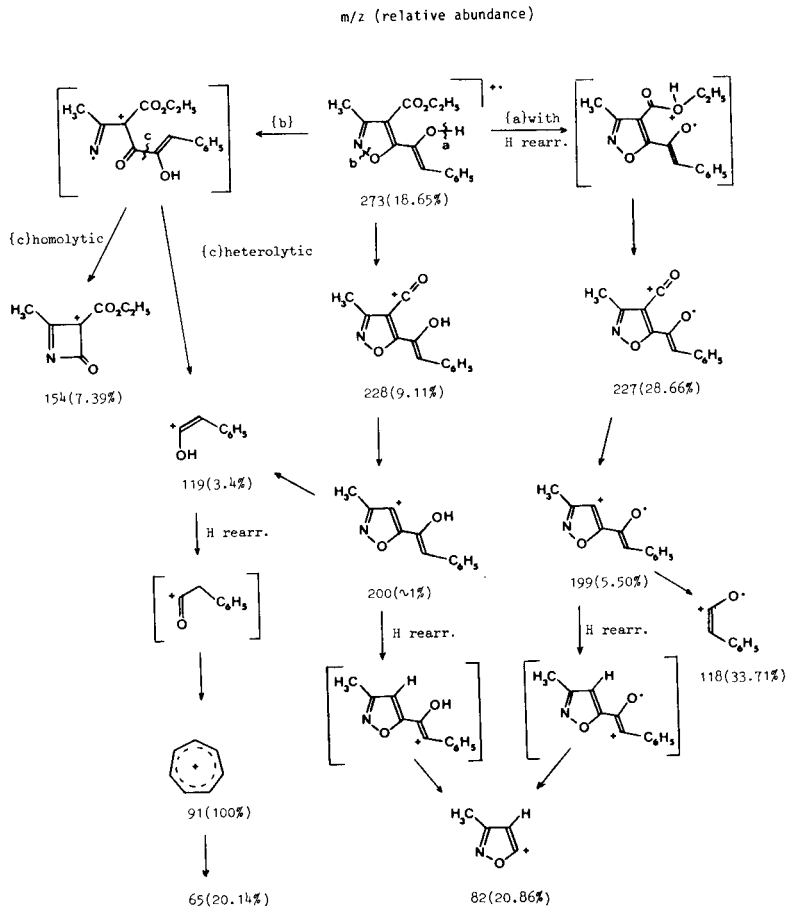


Table 2

[1] H-NMR Spectral Data of Compounds **7**, **14**, and **18** in Deuteriochloroform

Compound No.	
7a	1.42 (t, 3H, J = 7 Hz), 2.55 (s, 3H), 4.47 (q, 2H, J = 7 Hz), 10.38 (s, 1H)
7b	1.35 (t, 3H, J = 7 Hz), 2.45 (s, 3H), 2.65 (s, 3H), 4.37 (q, 2H, J = 7 Hz)
7c	0.97 (s, 3H, J = 7 Hz), 2.57 (s, 3H), 4.10 (q, 2H, J = 7 Hz), 7.30-8.16 (m, 5H)
7d	1.27 (s, 3H, J = 7 Hz), 2.61 (s, 3H), 4.33 (q, 2H, J = 7Hz), 7.27-7.87 (m, 5H)
14a [a]	1.37 (t, 3H, J = 7.1 Hz), 2.38 (s, 3H), 4.37 (q, 2H, J = 7.1 Hz), 6.48 (d, 1H, J = 1.6 Hz, [b]), 7.23 (t, 1H, J = 7.4 Hz), 7.35 (t, 2H, J = 7.4 Hz), 7.84 (d, 2H, J = 7.4 Hz), 11.01 (d, 1H exchangeable with deuterium oxide, J = 1.6 Hz)
14b	1.42 (t, 3H, J = 7 Hz), 2.44 (s, 3H), 3.82 (s, 3H), 4.43 (q, 2H, J = 7 Hz), 6.49 (br s [c], 1H), 6.90 (d, 2H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.8 Hz), 10.80 (br s [c], 1H exchangeable)
14c	1.44 (t, 3H, J = 7 Hz), 2.46 (s, 3H), 4.45 (q, 2H, J = 7 Hz), 6.46 (d, 1H, J = 1.8 Hz), 7.31 (d, 2H, J = 8.6 Hz), 7.80 (d, 2H, J = 8.6 hz), 11.07 (d, 1H exchangeable, J = 1.8 Hz)
18	1.38 (t, 3H, J = 7 Hz), 2.35 (s, 3H), 3.50-3.90 (m, 8H), 4.35 (q, 2H, J = 7 Hz), 6.27 (s, 1H), 9.42 (s, 1H exchangeable)

[a] 300 MHz spectrum, [b] The resonance appears as a singlet by irradiation at δ 11.01. [c] The signal is significantly broadened by the ethylenic-hydroxylic protons coupling.

changeable proton were coupled together (J = 1.6 Hz). The formation of three different heterocycles could be expected by ring closure of the open chain intermediate **10**: a 1,2-oxazine derivative **11**, or **12**, a *N*-hydroxypyrrolinone **13** or an isoxazole **14**. Although structures **11**, **12** and **13** did not seem very likely because of the coupling between the ethylenic and exchangeable protons, the attribution of structure remained uncertain. The formulation of the product as the ethyl 5-(1-hydroxy-2-phenylethenyl)-3-methylisoxazole-4-carboxylate (**14a**) resulted from its reduction with sodium borohydride which yielded the ethyl 5-(1-hydroxy-2-phenylethyl)-3-methylisoxazole-4-carboxylate (**16**). The structure of compound **16** was consistent with the microanalytical, ^{1}H-nmr and ir data (see experimental) and was firmly established by examination of the ^{13}C-nmr spectrum (Table 7). The observed chemical shifts for C-3, C-4 and C-5 of the isoxazole ring are entirely similar to our reported values for ethyl 5-(1-hydroxyalkyl)isoxazole-4-carboxylates [4]. In particular the positions of the nitrogen and oxygen in the ring are unambiguously established and this result is in agreement with a primary attack of the nitrogen of hydroxylamine at C-5 of the arylidenefuranone **8** as supposed in the structure of the open chain intermediate **10**. The ^{13}C-nmr data of the enol **14a** fits well with an isoxazolic structure as it appears from the comparison of C-3, C-4 and C-5 chemical shifts of this compound with those of ketone **7b** and alcohol **16** (Table 7). Examination of the ^{13}C-nmr coupled spectrum of compound **14a** showed that C-5 and C-1′ were triplets and C-2′ a doublet of quadruplets. The observed multiplicities are partly due to long-range couplings (^{2}J or ^{3}J) between these carbons and the hydroxylic proton. In addition to the long-range coupling between the hydroxylic and ethylenic protons, these results suggest that the rate of hydroxylic proton exchange is slow with regard to spectra averaging. Apart from electronic factors, the chelation of the hydroxylic proton could be involved in the stabilization of the enol form **14a** and explain the striking difference observed in the position of the keto-enol "equilibrium" when the ring is an isoxazole (enol form **14a** only) or a pyrazole (keto form **9** only [6]). After examination of the Dreiding stereomodels of keto and enol forms, it appeared that the ketonic structure of pyrazoles **9** could be stabilized by hydrogen bonding between the pyrazolic proton and the oxygen of the carbonyl group. On the contrary, hydrogen bonding of the hydroxylic proton with the oxygen of the ring could be responsible for the enolic structure of isoxazole **14a**. The long-range coupling of 1.6 Hz between the ethylenic and hydroxylic protons is consistent with an unsaturated system incorporating a planar W-path [7] as illustrated in Scheme B. This leads to the assignment of a Z configuration for compound **14a**, in agreement with the steric hindrance of the phenyl group. A plausible fragmentation pattern for the main peaks of the low-resolution 70 eV EI mass spectrum of

Table 3

Physical Data for Isoxazolo [4,5-*d*]pyridazin-4(5*H*)-ones **20**

Compound No.	Yield (%)	Mp (°C) (Solvent)	Molecular Formula	Analyses % Calcd./Found C	H	N	IR(cm^{-1}) (Chloroform)	UV (Ethanol) λmax (ε max)
20a	67 [a]	230 ethanol	$C_7H_7N_3O_2$	50.91 50.61	4.27 4.26	25.45 25.60	3300-2800, 1700, 1615 [e]	283 (4400)
20b	66 [a]	243 ethanol	$C_{12}H_9N_3O_2$	63.43 63.29	3.99 3.95	18.49 18.47	3300-2600, 1700, 1605 [e]	251 (29000) 305(7500)
20c	79 [a]	208 ethanol	$C_{12}H_9N_3O_2$	63.43 63.57	3.99 3.97	18.49 18.72	3300-2700, 1680, 1605 [e]	237 (14400) 280 (5200)
20d	72 [a]	124 hexane/ethyl acetate 3:7	$C_{13}H_{11}N_3O_2$	64.72 64.46	4.60 4.58	17.42 17.42	1690, 1615 [f]	303 (7300)
20e	70 [a]	176 hexane/ethyl acetate 3:7	$C_{18}H_{13}N_3O_2$	71.27 71.25	4.32 4.26	13.86 13.74	1690, 1610 [f]	249 (24400) 325 (10200)
20f	70 [a]	110 hexane/ethyl acetate 1:9	$C_{14}H_{13}N_3O_2$	65.87 65.53	5.13 5.06	16.46 16.54	1690, 1615 [f]	295 (6500)
20g	48 [a]	163 hexane/ethyl acetate 1:4	$C_{19}H_{15}N_3O_2$	71.91 72.20	4.76 4.81	13.24 13.21	1690, 1600 [f]	251 (24200) 317 (8900)
20h	85 [b]	179 ethanol	$C_{13}H_{11}N_3O_2$	64.72 64.54	4.60 4.58	17.42 17.49	3300-2600, 1680, 1605 [e]	212 (23300) 288 (4500)
20i	74 [b]	176 ethanol	$C_{14}H_{13}N_3O_3$	61.98 61.74	4.83 4.56	15.49 15.72	3300-2600, 1690, 1610 [e]	214 (25300) 282 (6800)
20j	67 [b]	202 ethanol	$C_{13}H_{10}N_3O_2Cl$ [d]	56.64 56.46	3.66 3.64	15.24 15.17	3300-2600, 1690, 1605 [e]	217 (26300) 288 (4600)
20k	73 [c]	208 dec ethanol	$C_{11}H_{14}N_4O_3$	52.79 52.50	5.64 5.69	22.39 22.34	3300-2600, 1680, 1610 [e]	213 (18900) 288 (4700)

[a] From compounds **7**. [b] From compounds **14**. [c] From compound **18**. [d] Cl analysis %, Calcd./Found: 12.86/12.87. [e] Potassium bromide. [f] Chloroform.

compound **14a** is proposed in Scheme F. Compounds **14b,c** prepared from 2-(4-methoxy-(or chloro)-benzylidene)-3(2*H*)-furanones **8b,c** displayed a similar structure as indicated by the spectral data (Tables 1 and 2).

An enolic structure was also observed when the bromoketone **17**, prepared by bromination of ketone **7b**, was reacted with morpholine (Scheme C). The product obtained was the ethyl 5-(1-hydroxy-2-morpholinoethenyl)-3-methylisoxazole-4-carboxylate (**18**) as shown by the microanalytical and spectral data (Tables 1 and 2) and not the corresponding keto form **19**.

When compounds **7b-d**, **14a-c** and **18** were treated with various hydrazines, the isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones **20a-k** were easily formed (Scheme D). The structures of compounds **20** were consistent with the microanalytical and spectral data (Tables 3 and 4). Reaction of the aldehyde **7a** with phenylhydrazine resulted in the exclusive formation of the phenylhydrazone **22a** (Scheme E); this hydrazone remained unchanged by refluxing six hours in acetic acid. When the aldehyde **7a** was submitted to the action of hydrazine hydrate in ethanol, either at room temperature or by refluxing two hours, two products were detected in the crude reaction mixtures. The major product (70 to 80%) was the hydrazone **22b** which could be partly isolated by filtration from ethanol. The minor product could be the expected isoxazolopyridazinone (^{1}H-nmr signals at δ 2.57 for the methyl group and δ 8.65 for the proton at C-7), but unfortunately complete separation from the hydrazone **22b** was not possible. By heating in acetic acid, the hydrazone **22b** was transformed in unidentified products. The reactivity of the aldehyde **7a** towards

Scheme E

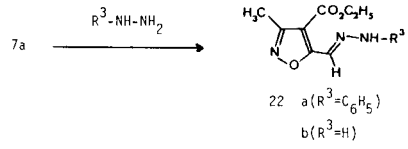


Table 4

^{1} H-NMR Spectral Data of Compounds 20

Compound No.	
20a	2.40 (s, 3H), 2.48 (s, 3H), 10.31 (br, 1H exchangeable with trifluoroacetic acid) [a]
20b	2.60 (s, 3H), 7.43-7.75 (m, 3H), 7.85-8.20 (m, 2H) [a] [b]
20c	2.53 (s, 3H), 7.48-7.75 (m, 3H), 8.25-8.45 (m, 2H), 13.05 (br, 1H exchangeable [a]
20d	2.58 (s, 3H), 2.65 (s, 3H), 7.33-7.73 (m, 5H), [c]
20e	2.68 (s, 3H), 7.27-7.87 (m, 8H), 8.10-8.40 (m, 2H) [c]
20f	2.53 (s, 3H), 2.63 (s, 3H), 5.35 (s, 2H), 7.16-7.64 (m, 5H) [c]
20g	2.66 (s, 3H), 5.47 (s, 2H), 7.13-7.73 (m, 8H), 8.07-8.37 (m, 2H) [c]
20h	2.53 (s, 3H), 4.20 (s, 2H), 7.29 (s, 5H), 13.03 (br, 1H exchangeable) [a]
20i	2.53 (s, 3H), 3.72 (s, 3H), 4.12 (s, 2H), 6.87 (d, 2H, J = 8.6 Hz), 7.23 (d, 2H, J = 8.6 Hz), 13.10 (br, 1H exchangeable) [a]
20j	2.55 (s, 3H), 4.22 (s, 2H), 7.36 (s, 4H), 13.06 (br, 1H exchangeable) [a]
20k	2.33 -2.66 (m, 7H with a singlet at 2.56), 3.45-3.80 (m, 6H with a singlet at 3.69), 13.10 (br, 1H exchangeable) [a]

[a] In $DMSOd_6$. [b] N*H* was not observed. [c] In deuteiochloroform.

Table 5

Physical Data for 4–Acyl-5-hydroxy-3(2*H*)-pyridaziones **21**

Compound No.	Yield %	Mp (°C) (solvent)	Molecular Formula	Analyses % Calcd./Found C	H	N	IR (cm^{-1}) (Potassium bromide)	UV (Ethanol) λmax (εmax)
21a	69	242	$C_7H_8N_2O_3$	50.00	4.80	16.66	3200-2500,	281 (4400)
		ethanol		50.02	4.78	16.55	1660, 1610	314 (4600)
21b	70	228	$C_{12}H_{10}N_2O_3$	62.60	4.38	12.17	3200-2600,	235 (19500)
		ethanol		62.21	4.23	12.23	1660, 1620	297 (7400)
21c	40	207	$C_{12}H_{10}N_2O_3$	62.60	4.38	12.17	3200-2600,	251 (11700)
		ethanol		62.27	4.30	12.03	1660, 1605	280 sh (6300)
								330 sh (3200)
21h	70	198	$C_{13}H_{12}N_2O_3$	63.92	4.95	11.47	3200-2600,	282 (5700)
		ethanol		63.97	4.87	11.51	1670, 1630	310 (5600)
21k	29	254-258 dec	$C_{11}H_{15}N_3O_4$	52.15	5.97	16.59	3520, 3450,	291 (5000)
		water		51.81	6.09	16.59	1650, 1630, 1610	314 (5700)

Table 6

^{1}H NMR Spectral Data of Compounds **21**

Compound No.	
21a	2.18 (s, 3H), 2.66 (s, 3H), 12.77 (br, 1H exchangeable with trifluoroacetic acid) [a]
21b	2.72 (s, 3H), 7.35-7.60 (m, 3H), 7.60-7.85 (m, 2H), 13.23 (br, 1H exchang) [a]
21c	2.21 (s, 3H), 7.38-7.76 (m, 3H), 7.76-8.05 (m, 2H), 12.54 (br, 1H exchang) [a]
21h	2.66 (s, 3H), 3.93(s, 2H), 7.26(s, 5H), 12.93 (br, 1H exchang) [a]
21k	2.50 (s, 3H), 3.25-3.60 (m, 4H), 3.90-4.20 (m, 4H), 4.24 (s, 2H) [b]

[a] In DMSO-d_6; only one exchangeable proton was observed. [b] In deuterium oxide.

Table 7

Pertinent ^{13}C–NMR Spectral Data of Compounds **7b**, **14a**, **16** (Deuteriochloroform) (δ ppm [a])

Compound No.	5-Substituent	C-1'	C-2'	C-3	C-4	C-5
7b	$\overset{1'\ 2'}{-CO-CH_3}$	187.6 [b]	28.9 [e]	160.2 [h]	113.0 [i]	166.4 [i]
14a	$\overset{1'\ 2'}{-C(OH)=CH-C_6H_5}$	140.0 [c]	111.4 [f]	160.0 [h]	107.9 [i]	170.8 [j]
16	$\overset{1'\ 2'}{-CH(OH)-CH_2-C_6H_5}$	68.5 [d]	41.7 [g]	159.6 [h]	109.0 [i]	178.9 [k]

[a] Determined by examination of the coupled spectra. [b] q, ^2J = 6.7 Hz. [c] t, ^2J = 3.2 Hz. [d] dt, ^1J = 150.0 Hz, ^2J = 5.1 Hz. [e] q, ^1J = 129.5 Hz. [f] dq, ^1J = 149.4 Hz, ^3J = 4.4 Hz. [g] td, ^1J = 129.0 Hz, ^2J = 3.6 Hz. [h] q, ^2J = 7 Hz. [i] s. [j] t, ^3J = 2.5 Hz. [k] d, ^2J = 3.1 Hz.

hydrazines can be explained by the lack of steric hindrance of the aldehydic proton, leading to the preferential formation of hydrazones of configuration anti which cannot cyclizise to isoxazolopyridazinones.

The reductive ring opening of the isoxazolopyridazinones **20a-c,h,k** followed by alkaline hydrolysis of the intermediate enamines gave rise to the 4-acyl-5-hydroxy-3(2*H*)-pyridazinones **21a-c,h,k** (Scheme D). The structures of compounds **21** were consistent with the microanalytical and spectral data (Tables 5 and 6).

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus. The infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and Perkin-Elmer 552 spectrometers. The nmr spectra were recorded on Brücker WP 80 and Brücker AM 300 spectrometers. The low-resolution mass spectrum was recorded on Nermag-10-10 S equipped with a SIDAR data system at an ionizing energy of 70 eV, and an ion source temperature of 130°. The chemical shifts reported are in parts per million from internal TMS. Elemental Analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

The following compounds were prepared as previously described: ethyl 3-methylamino-2-butenoate [5], acyl chlorides **5a** [8], **b,c** [9], ethyl 5-(1-hydroxyethyl)-3-phenylisoxazole-4-carboxylate **2d** [4], and 2-arylidene-4-ethoxycarbonyl-5-methyl-3(2*H*)-furanones **8a-c** [10].

Ethyl 5-(1-Hydroxyalkyl)-3-methylisoxazole-4-carboxylates **2a,b** and Ethyl 5-(Hydroxyphenylmethyl)-3-methylisoxazole-4-carboxylate (**2c**). General Procedure.

To a stirred solution of ethyl 3-methylamino-2-butenoate (**4**) (28.6 g, 0.2 mole) and pyridine (16 ml, 0.2 mole) in anhydrous ethyl ether (400 ml), cooled in a water-ice bath, was added dropwise a solution of α-acetoxy acyl chloride **5** (0.21 mole) in anhydrous ethyl ether (150 ml). The resulting mixture was stirred overnight at room temperature. The ethereal solution was washed three times with 100 ml of water and dried over anhydrous sodium sulfate. The solvent was evaporated to yield crude compound **6** which was dissolved in acetic acid (400 ml). Hydroxylamine hydrochloride (13.9 g, 0.2 mole) was added and the mixture was refluxed for 30 minutes. Acetic acid was evaporated *in vacuo* and ethyl ether was added (300 ml). The solution was washed with water, saturated sodium bicarbonate solution, water and dried. Ethyl ether was evaporated. The residue was dissolved in an ethanolic solution of hydrogen chloride, prepared from absolute ethanol (600 ml) and acetyl chloride (30 ml), and refluxed for 30 minutes. After removal of ethanol, the residue was dissolved in ethyl ether (200 ml). The ethereal solution was washed with saturated sodium bicarbonate solution, water, dried over anhydrous sodium sulfate and evaporated. The residue was distilled

under reduced pressure to afford isoxazoles **2**. Yields from **4** were: **2a** (58%, bp 130-132°/2 torr); **2b** (52%, bp 122-125°/1.5 torr); **2c** (65%, bp 184-186°/2 torr).

Ethyl 5-Formyl-3-methylisoxazole-4-carboxylate (**7a**, Tables 1 and 2).

A mixture of isoxazole **2a** (10 g, 0.054 mole) in dichloromethane (200 ml) and pyridinium chlorochromate [11] (17.7 g, 0.082 mole) was stirred for 3 days at room temperature. Ethyl ether (200 ml) was added to the reactional mixture and the supernatant liquid was passed through a short column of silicagel (85 g) and anhydrous sodium sulfate (85 g). The column was washed three times with ethyl ether (100 ml). The solvent was evaporated to give crude compound **7a** (8.3 g). This procedure was repeated four times and the combined residues were purified by fractional distillation under reduced pressure with a spinning band column to give pure compound **7a**.

Ethyl 5-Acetyl(or benzoyl)isoxazole-4-carboxylates **7b-d** (Tables 1 and 2).

To a cooled and stirred solution of isoxazole **2b-d** (0.1 mole) in acetone (500 ml) was added dropwise Jones'reagent (50 ml, prepared from 13.4 g of chromium trioxide, 10.6 ml of 36 *N* sulfuric acid and water). The mixture was stirred for 4 hours at room temperature. The precipitated salts were filtered off, washed with acetone and the combined acetone layers were stirred with solid sodium bisulfite to destroy the excess of Jones'reagent. The solution was filtered and acetone was evaporated *in vacuo*. The residue was diluted with water (300 ml) and extracted three times with dichloromethane (100 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution, water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure to give pure compounds **7b,d**; in the case of **7c**, the solid residue was quite pure and an analytical sample was obtained by recrystallization from ethanol.

Ethyl 5-(2-Aryl-1-hydroxyethenyl)-3-methylisoxazole-4-carboxylates **14a-c**, (Tables 1 and 2). General Procedure.

A mixture of 3-(2*H*)-furanone **8** (10 mmoles), sodium acetate (1.63 g, 12 mmoles), hydroxylamine hydrochloride (0.76 g, 11 mmoles), water (10 ml) and ethanol (50 ml for **8a**, 70 ml for **8b**, 130 ml for **8c**) was refluxed for 2 hours. After cooling, the yellow crystals of **14** were collected and dried. Analytical samples were obtained by recrystallization from ethanol.

Ethyl 5-(1-Hydroxy-2-phenylethyl)-3-methylisoxazole-4-carboxylate (**16**).

To a stirred solution of **14a** (1 g, 3.66 mmoles) in methanol (300 ml) was added sodium borohydride (0.38 g, 10 mmoles) in small portions. After 15 minutes, the mixture was cooled and the excess of sodium borohydride was destroyed by addition of acetic acid (1 ml). The solvent was evaporated *in vacuo* and water was added (20 ml). The mixture was extracted with dichloromethane. The organic layer was washed with water, saturated sodium bicarbonate solution, water and dried over anhydrous sodium sulfate. After removal of the solvent the residue was recrystallized from hexane/ethyl acetate 4:1 to give pure **16**, Yield 0.81 g (80%), mp 74°; ir (chloroform): 3380, 1715 (sh), 1690, 1600 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7 Hz), 2.42 (s, 3H), 3.18 (d, 2H, J = 7 Hz), 4.17-4.57 (q, 2H, J = 7 Hz + 1H exchangeable with trifluoroacetic acid), 5.28 (q, 1H, J = 7 Hz, the quadruplet was transformed to a triplet with TFA), 7.24 (s, 5H), ^{13}C-nmr spectral data are given in Table 7.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.61; H, 6.28; N, 5.16.

Ethyl 5-Bromoacetyl-3-methylisoxazole-4-carboxylate (**17**).

To a stirred solution of **7b** (7.88 g, 0.04 mole) in chloroform (120 ml) heated to reflux was added dropwise a solution of bromine (6.56 g, 0.041 mole) in chloroform (15 ml). Refluxing was continued for 15 minutes. The solvent was evaporated *in vacuo* to give crude bromoketone **17** (14.5 g) as a liquid which can be used in the following step without further purification. The bromoketone **17** was characterized by its ^{1}H-nmr spectrum (deuteriochloroform): δ 1.37 (t, 3H, J = 7 Hz), 2.47 (s, 3H), 4.37 (q, 2H, J = 7 Hz), 4.50 (s, 2H).

Ethyl 5-(1-Hydroxy-2-morpholinoethenyl)-3-methylisoxazole-4-carboxylate (**18**, Tables 1 and 2).

A solution of morpholine (14 ml, 0.16 mole) in chloroform (20 ml) was added to a stirred solution of crude bromoketone **17** (14.5 g) in chloroform (150 ml). The mixture was refluxed for 1.5 hours. After cooling, the mixture was washed three times with water and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue recrystallized from ethanol to give pure compound **18** (5.8 g).

Isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones **20a-c,h-k** (Tables 3 and 4). General Procedure.

A mixture of **7b-d**, **14a-c** or **18** (5 mmoles), hydrazine hydrate (0.5 ml, 10 mmoles) and ethanol (10 ml for **7b-d**, **14a**, 25 ml for **14b**, 46 ml for **14c**, 35 ml for **18**) was stirred at room temperature for 4 hours for **7b-d** or refluxed for 2 hours for **14a-c** or 6 hours for **18**. After cooling, the white precipitate was collected and recrystallized from ethanol to give pure compounds **20a-c,h-k**.

5-Benzyl or 5-Phenylisoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones **20d-g** (Tables 3 and 4). General Procedure.

A mixture of **7b,c** (5 mmoles), phenylhydrazine or benzylhydrazine (5.2 mmoles) and acetic acid (10 ml) was refluxed for 3 hours. Acetic acid was evaporated *in vacuo* and the solid residue was recrystallized from a suitable solvant to give pure compounds **20d-g**.

4-Acyl-5-hydroxy-3(2*H*)-pyridazinones **21a-c,h,k** (Tables 5 and 6). General Procedure.

A solution of **20a-c,h,k** (5 mmoles) in ethyl acetate (250 ml) and ethanol (50 ml) was hydrogenated with 5% palladium on carbon (1 g) at room temperature using a low pressure hydrogenation apparatus (*ca.* 1 atmosphere). After uptake of the calculated amount of hydrogen, the catalyst was filtered off and the solvent evaporated *in vacuo*. The residue was refluxed for 2 minutes for **21h** or 10 minutes for **21a-c**, or stirred at room temperature for 2 hours for **21k** in 0.5 *N* aqueous potassium hydroxide (65 ml). After cooling and filtration, the solution was acidified to *p*H = 2 in the case of **21a-c,h** or to *p*H = 7 in the case of **21k** with 10% sulfuric acid. The compounds **21a-c,h** were obtained by filtration followed by recrystallization from ethanol. In the case of **21k**, the neutral aqueous solution was evaporated to dryness *in vacuo*. The residue was refluxed with absolute ethanol (180 ml) and filtered. Ethanol was evaporated *in vacuo* to give crude compound **21k** which was recrystallized from water.

Ethyl 5-Phenylhydrazinomethine-3-methylisoxazole-4-carboxylate **22a**.

Phenylhydrazine (0.5 ml, 5.2 mmoles) was added to a solution of **7a** (0.92 g, 5 mmoles) in acetic acid (10 ml). The mixture was stirred for 2 hours at room temperature. The phenylhydrazone **22a** was collected by filtration and washed with cold ethanol. An analytical sample was obtained by recrystallization from ethanol, yield 1.17 g (85%); mp 184°; ir (potassium bromide): 3440, 3200, 1720, 1600 cm^{-1}; ^1H-nmr (DMSO-d_6): 1.36 (t, 3H, J = 7 Hz), 2.41 (s, 3H), 4.34 (q, 2H, J = 7 Hz), 6.84-7.50 (m, 5H), 8.30 (s, 1H), the N*H* resonance was not observed.

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.21; H, 5.61; N, 15.32.

Ethyl 5-Hydrazinomethine-3-methylisoxazole-4-carboxylate (**22b**).

Hydrazine hydrate (0.6 ml, 12 mmoles) was added to a solution of **7a** (1.15 g, 6.3 mmoles) in ethanol (10 ml). The mixture was refluxed for 2 hours. After cooling the hydrazone **22b** was collected by filtration. An analytical sample was obtained by recrystallization from ethanol, yield 0.79 g (64%), mp 156°; ir (potassium bromide): 3400, 3200, 1690, 1600 cm^{-1}; ^1H-nmr (DMSO-d_6): 1.32 (t, 3H, J = 7 Hz), 2.35 (s, 3H), 4.26 (q, 2H, J = 7 Hz), 8.02 (s, 1H). 8.44 (s, 2H exchangeable with deuterium oxide).

Anal. Calcd. for $C_6H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.64; H, 5.44; N, 21.39.

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