PYRANOISOXAZOLE SYSTEMS. SYNTHESIS OF 3-OXO-6,7-DIHYDRO-3*H*,7a*H*-PYRANO[4,3-c]ISOXAZOLES AND 4-OXO-3,6,6-TRIMETHYL-3a,6,7,7a-TETRAHYDRO-4*H*-PYRANO[4,3-c]ISOXAZOLE

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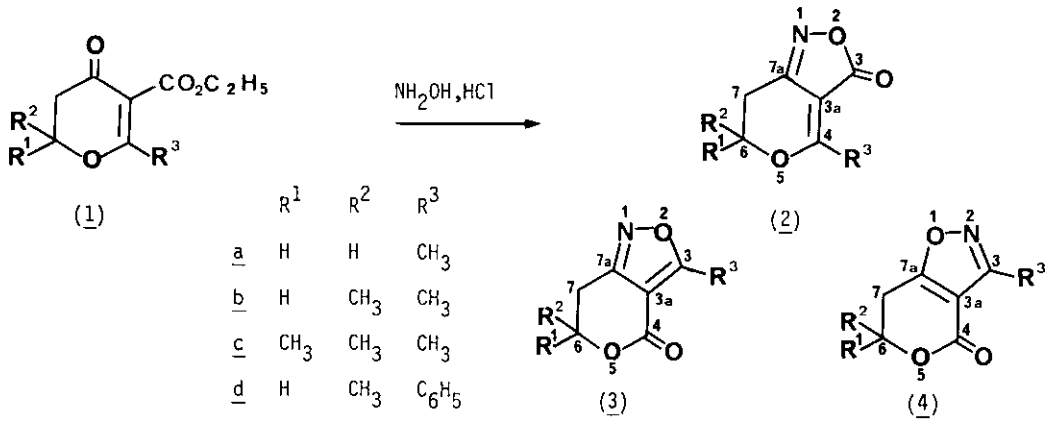
Abstract —— The reaction of hydroxylamine with 2,3-dihydropyran-4-ones provides a route to 3-oxo-6,7-dihydro-3*H*,7a*H*-pyrano[4,3-c]isoxazole derivatives. In addition, the spectral properties of a representative series of the three possible isomeric isoxazoles having a fused-pyran ring was investigated.

In the course of our work on the potentiality of 2,3-dihydropyran-4-ones (1), as starting material for novel heterocyclic systems[1-4], we wish to report the synthesis of the new fused-ring isoxazoles (2a-e) and (3c).

In the reaction of dihydropyran-4-ones (1) with hydroxylamine, one could envisage the formation of three possible compounds, (2), (3), or (4). In fact, the products obtained by reacting (1a-e) with hydroxylamine hydrochloride, in refluxing propanol or acetic acid, were identified as the hitherto unknown 3-oxo-6,7-dihydro-3*H*,7a*H*-pyrano[4,3-c]isoxazoles (2a-e).

Scheme I



(1)

	R^1	R^2	R^3
a	H	H	CH_3
b	H	CH_3	CH_3
c	CH_3	CH_3	CH_3
d	H	CH_3	C_6H_5
e	CH_3	CH_3	C_6H_5

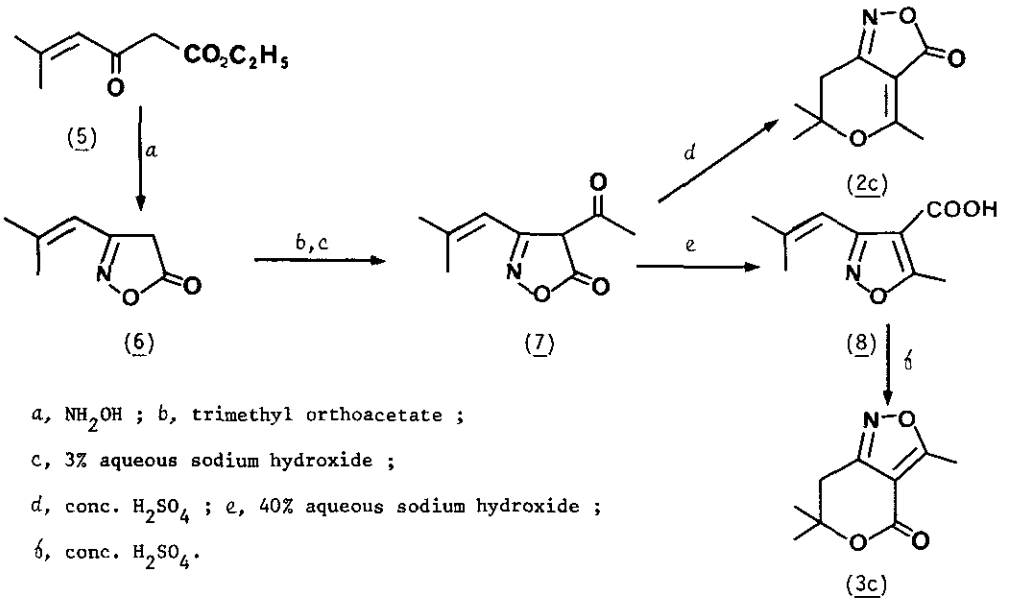
(2) (3) (4)

Compounds (2) were likely formed by an initial oxime formation at the ketone function of the dihydropyran-4-ones (1). No product derived from a nucleophilic addition at C-2, leading to ring-opening ring-closure rearrangement to afford compounds (3) or (4) was observed[5].

The structure of compounds (2) was established by analytical data and by alternate synthesis of (2c). This was accomplished by cyclization of 4-acetyl-3-(2-methyl-1-propenyl)isoxazol-5-one (7). The synthesis of (7) previously unknown, was realized from ethyl 5-methyl-3-oxo-4-hexenoate (5) by a procedure similar to that described for making 4-acetyl-3-phenylisoxazol-5-one[6] (scheme 2).

On the other hand, compound (7) was a useful precursor for a regiospecific access to new 4-oxo-3,6,6-trimethyl-3a,6,7,7a-tetrahydro-4H-pyrano[4,3-c]isoxazole (3c), isomer of (2c), via 5-methyl-3-(2-methyl-1-propenyl)-4-carboxylic acid (8) (scheme 2). As we recently reported on the preparation of the other isomer (4c)[7], this series of the three isomers provides an opportunity to compare their spectroscopic data (table 2).

Scheme 2



a, NH_2OH ; b, trimethyl orthoacetate ;
c, 3% aqueous sodium hydroxide ;
d, conc. H_2SO_4 ; e, 40% aqueous sodium hydroxide ;
f, conc. H_2SO_4.

The differences in the ^{1}H-NMR spectra were not conclusive in determining the structure of these isomers. However, the ^{13}C-NMR study has proven quite valuable to distinguish between these isomeric pyranoisoxazoles. We can see (table 2) by comparing the carbon chemical shifts between the isomers, that the carbon adjacent to an oxygen is significantly deshielded as compared to the one which bears the isoxazole nitrogen. These findings might be useful in making assignment in other condensed isoxazoles, since little work has been done on the ^{13}C-NMR information on isomeric isoxazoles[8-10] and isoxazol-5-ones[11,12].

Table 1 . Preparation of compounds (2)

Compd.	Yield %	mp (°C) (Solvent)	Molecular Formula[a]	IR ($CHCl_3$) νC=O (cm^{-1})	UV (Ethanol) λmax(nm)(ε)	^{1}H-NMR ($CDCl_3$) δ (ppm)
(2a)	23	116-117 ethanol/water 1:1	$C_7H_7NO_3$ (153.2)	1750 1770	290 (8700)	2.46 (s,3H); 3.02 (t,2H, J=7 Hz); 4.63 (t,2H, J=7 Hz).
(2b)	45	113-114 ethanol/water 1:1	$C_8H_9NO_3$ (167.2)	1750	295 (9000)	1.62 (d,3H,J=6 Hz); 2.45 (s,3H); 2.68 (dd,1H, J=17 Hz,11 Hz)[b]; 3.05 (dd,1H,J=17 Hz,5 Hz)[b]; 4.65 (m,1H).
(2c)	55	114-115 ethanol/water 1:1	$C_9H_{11}NO_3$ (181.2)	1755	295 (9500)	1.53 (s,6H); 2.41 (s,3H); 2.87 (s,2H).
(2d)	43	137-139 ethanol	$C_{13}H_{11}NO_3$ (229.2)	1755	264 (9700) 342 (10600)	1.67 (d,3H,J=6 Hz); 2.72 (dd,1H,J=17 Hz,11 Hz)[b]; 3.05 (dd,1H,J=17 Hz,5 Hz)[b]; 4.70 (m,1H); 7.3-7.7.(m,3H); 8.27 (dd,2H,J=8 Hz,2 Hz).
(2e)	55	150-151 ethanol	$C_{14}H_{13}NO_3$ (243.2)	1755	262 (9500) 344 (10300)	1.62 (s,6H); 2.95 (s,2H); 7.3-7.7 (m,3H); 8.27 (dd, 2H,J=8 Hz,2 Hz).

[a] Satisfactory microanalyses obtained: C ± 0.18; H ± 0.05; N ± 0.13.

[b] ABX system in first order treatment.

Table 2 . Pertinent spectral data of (2c), (3c), and (4c)

Compd.	^{13}C-NMR (δ ppm,$CDCl_3$)[a]						^{1}H-NMR (δ ppm,$CDCl_3$)			IR ($CHCl_3$)
	C-3	C-3a	C-4	C-6	C-7	C-7a	CH_3(C-4 or C-3)	CH_2(C-7)	$(CH_3)_2$(C-6)	νC=O(cm^{-1})
(2c)	169.3	97.0	177.2[b]	85.2	33.4	155.4[c]	2.41 (s)	2.87 (s)	153 (s)	1755
(3c)	174.3[d]	104.1	160.1	82.9	32.6	159.6[e]	2.74 (s)	3.01 (s)	1.52 (s)	1735
(4c)	157.9[b]	105.0	160.1	82.3	34.5	175.6[f]	2.51 (s)	3.12 (s)	1.57 (s)	1740

[a] The carbon shifts were assigned from the multiplicity in the off-resonance decoupled spectra and examination of the coupled spectra. [b] quadruplet, ^2J = 6.5 Hz ; [c] triplet, ^2J = 7.5 Hz ; [d] quadruplet, ^2J = 7 Hz ; [e] triplet, ^2J = 7 Hz ; [f] triplet, ^2J = 8 Hz.

EXPERIMENTAL SECTION

All melting points were determined on a Kofler block. Infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and DB spectrometers. NMR spectra were recorded on a Brucker WP 80 and on a Varian XL 100 12 FT spectrometers. Elemental analyses were performed by Micro-analytical laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

Compounds (1a-e)[13] and (4c)[7] were prepared as previously described.

3-Oxo-6,7-dihydro-3*H*,7a*H*-pyrano[4,3-c]isoxazoles (2a-e). General Procedure

A mixture of 5-ethoxycarbonyl-2,3-dihydropyran-4-one (1) (20 mmol), hydroxylamine hydrochloride (1.5 g, 21.6 mmol), in *n*-propanol (50 ml) or acetic acid (50 ml) in the case of (2a) and (2b), was refluxed for 1 h (or 0.5 h in acetic acid). After evaporation under reduced pressure of the solvent, the residue was extracted into chloroform. The chloroform solution was washed with 10% sodium hydrogen carbonate solution (20 ml), water (20 ml), dried and evaporated. The residue was then triturated with cold ether (5-10 ml) and the solid was collected by suction to give crude (2a-e). Analytical samples were obtained by recrystallization from a suitable solvent (table 1).

3-(2-Methyl-1-propenyl)isoxazol-5-one (6)

This compound was prepared from ethyl 5-methyl-3-oxo-4-hexenoate[14] by the literature method[15] described for 3-methylisoxazol-5-one with only slight modifications : methanol (250 ml/mol) was added to the reaction mixture; reaction time 4 h. Yield 30%; mp 58-59°C (hexane). IR ($CHCl_3$) νC=O: 1810 cm^{-1}. ^{1}H-NMR ($CDCl_3/TMS_{int}$) δ: 1.99 (d,3H,J= 1 Hz); 2.01 (d,3H,J=1 Hz); 3.57 (s,2H); 5.91 (m,1H). Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.39; H, 6.51; N, 10.16.

4-Acetyl-3-(2-methyl-1-propenyl)isoxazol-5-one (7)

This compound was prepared from (6) by the literature method[6]. Yield 60% ; mp 130-132°C (ethyl acetate/hexane 1:1). IR ($CHCl_3$) νC=O: 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3/TMS_{int}$) δ: 1.97 (m,6H); 2.40 (s,3H); 5.92 (m,1H); 9.66 (s,1H). Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.49; H, 6.09; N, 7.65.

3-Oxo-4,6,6-trimethyl-6,7-dihydro-3*H*-7a*H*-pyrano[4,3-c]isoxazole (2c) from (7)

Compound (7) (1.81 g, 0.01 mol) was added to concentrated sulfuric acid (40 ml), with stirring. The mixture was allowed to stand at room temperature for a night. The mixture was then poured on to ice water (400 g) and extracted with chloroform (3 X 50 ml). The combined extracts were washed with 10% potassium carbonate solution (2 X 20 ml), water (20 ml), dried and evaporated. The residue was triturated with cold ether (∿ 5 ml) and collected by suction to give crude (2c). Yield 1.27 g (70%).

5-Methyl-3-(2-methyl-1-propenyl)isoxazole-4-carboxylic acid (8)

This compound was prepared from (7) according to the literature method[6] described for the synthesis

of 5-methyl-3-phenylisoxazole-4-carboxylic acid from 4-acetyl-3-phenylisoxazol-5-one except that the reflux time was 12 h, using 40% aqueous sodium hydroxide. Yield 50%; mp 156-157°C (ethanol). IR ($CHCl_3$) νC=O: 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3/TMS_{int}$) δ: 2.01 (d,3H,J=1 Hz); 2.09 (d,3H,J=1 Hz); 2.72 (s,3H); 6.50 (m,1H); 10.0 (br. s,1H). Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.80; C, 6.29; N, 7.70.

4-Oxo-3,6,6-trimethyl-3a,6,7,7a-tetrahydro-4*H*-pyrano[4,3-c]isoxazole (3c)

Compound (8) (1 g, 5.5 mmol) was cyclized in concentrated sulfuric acid, as described above for the conversion of (7) to (2c). Yield 0.7 g (70%); mp 114-116°C (ethyl acetate/hexane 4:1). IR ($CHCl_3$) νC=O: 1735 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.36; H, 6.13; N, 7.74.

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