Synthesis of Some 3-Alkenyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazoles

Bernard Chantegrel, Abdel-Ilah Nadi and Suzanne Gelin*

Laboratoire de Chimie Organique, Institut National des Sciences Appliquées
F-69621 Villeurbanne Cedex, France

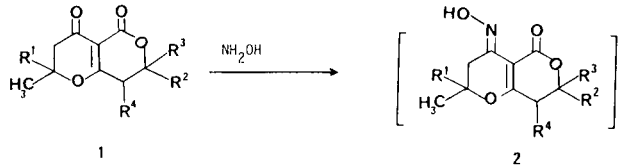
Received January 22, 1985

A series of 3-alkenyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole derivatives was prepared by reaction of hydroxylamine with 4,5-dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran derivatives.

J. Heterocyclic Chem., **22**, 1127 (1985).

A previous report from our laboratory has described the synthesis of some 3-methyl-4-oxo-6,7-dihydro-4*H*-pyrano-[3,4-*d*]isoxazole derivatives [1]. We have also reported on the identification of isomeric isoxazoles fused with a pyrone ring by ^{13}C-nmr examination [2]. Poursuing our research connected with obtaining biologically-active heterocycles, we wish to report on the synthesis of the new 3-alkenyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole derivatives **3a-e**.

Treatment of 4,5-dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyrans **1a-e** [3] with an excess of hydroxylamine,, in refluxing acetic acid, led to the pyranoisoxazoles **3a-e**. The reaction proceeds *via* the initial formation of the oximes **2**, as intermediates, which rearrange with ring opening of the dihydropyrones and recyclization to afford **3**. The intermediate oximes have been isolated under mild conditions. When the oxime **2a** [4] was heated in the presence of hydroxylamine in acetic medium, it gave the product **3a** in good yield.



1 2

	R^1	R^2	R^3	R^4
a	H	Me	H	H
b	H	H	H	Me
c	Me	Me	H	H
d	Me	H	H	Me
e	Me	Me	Me	H

3

The structure of compounds **3** was deduced through their analytical and spectral data (Tables 1 and 2). Unambiguous assignment of the [3,4-*d*] junction was supported by ^{13}C-nmr spectral comparison of **3a** (Figure 1) [5] with previous findings concerning the carbon chemical shifts of isomeric isoxazoles [2,6-9]. The carbon adjacent to an oxygen is deshielded as compared to the one which bears the isoxazole nitrogen.

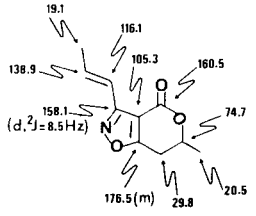


Figure 1

EXPERIMENTAL

All melting points were determined on a Kofler apparatus. The infrared spectra were recorded on a Beckman Acculab 2 spectrometer. The nmr spectra were recorded on a Brucker WP 80 and on a Varian XL 100 12 FT Spectrometers. Elemental analyses were performed by Microanalytical laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

4,5-Dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran derivatives **1**.

These compounds were prepared as previously described [3].

4-Hydroxyimino-5-oxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran (**2a**).

To a mixture of **1a** (1.96 g, 0.01 mole) and sodium acetate (1.64 g, 0.02 mole) in ethanol (40 ml) was added hydroxylamine hydrochloride (1.4 g, 0.02 mole) in water (15 ml). The reaction mixture was stirred at room temperature for 1 hour and then filtered. The crude compound **2a** was purified by recrystallization from ethanol, mp 198° dec; ir (chloroform): 3300 cm^{-1} (OH), 1720 (C=O); ^{1}H-nmr (DMSO-d$_6$): δ 1.33 (d, 3H, J = 6 Hz), 1.38 (d, 3H, J = 6 Hz), 2.0-2.7 (m, 3H), 3.2 (dd, 1H, J = 17 Hz, 3 Hz), 4.1-4.7 (m, 2H), 11.0 (s, 1H).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.10; N, 6.65.

3-Alkenyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole Derivatives **3**.

General Procedure.

A mixture of **1** (0.01 mole), acetic acid (40 ml), water (15 ml), sodium acetate (1.64 g, 0.02 mole) and hydroxylamine hydrochloride (1.4 g, 0.02 mole) was refluxed for 2 hours. The reaction mixture was then poured on to ice water (200 ml) and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with 10% potassium carbonate solution (2 × 50 ml) water (50 ml), dried and evaporated under reduced pressure to give the crude isoxazole **3**, which are further purified by column chromatography on silica gel using dichloromethane as eluent. Analytical sample was obtained by recrystallization from ethanol/water (1:1). Yields and physical data were summarized in the Tables 1 and 2.

3-Propenyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole (**3a**) from **2a**.

A mixture of **2a** (5 mmoles), acetic acid (20 ml), water (8 ml), sodium acetate (20 mmoles) and hydroxylamine hydrochloride (10 mmoles) was refluxed for 2 hours. The reaction mixture was then worked up as described above to give **3a**, yield, 0.77 g (70%).

In the pharmacological screening, compound **3a** displayed a broncho-

Table 1

Physical and Analytical Data for Compounds **3**

Compound No.	Yield % [a]	Mp°C	Molecular Formula	Analyses % (Calcd./Found) C	H	N	IR (Chloroform) ν C=O (cm^{-1})
3a	65	89-90	$C_{10}H_{11}NO_3$	62.16	5.74	7.25	1745
				62.37	5.71	7.21	
3b	60	46-47	$C_{10}H_{11}NO_3$	62.16	5.74	7.25	1750
				62.12	5.91	7.30	
3c	65	80-81	$C_{11}H_{13}NO_3$	63.75	6.32	6.76	1745
				63.63	6.49	6.52	
3d	70	95-96	$C_{11}H_{13}NO_3$	63.75	6.32	6.76	1745
				63.89	6.28	6.55	
3e	50	116-117	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	1745
				64.90	7.03	6.14	

[a] Yield after column chromatography.

Table 2

Proton Magnetic Resonance Parameters

Compound No.	Chemical shift (deuteriochloroform) δ (ppm)
3a	1.61 (d, 3H, J = 6 Hz), 1.96 (dd, 3H, J = 7 Hz, 1.2 Hz), 2.9 (dd, 1H, J = 17 Hz, 10 Hz) and 3.2 (dd, 1H, J = 17 Hz, 5 Hz) [a], 4.5-5.0 (m, 1H), 6.5 (dq, 1H, J = 16 Hz, 1.2 Hz) and 7.2 (dq, 1H, J = 16 Hz, J = 7 Hz) [b]
3b	1.43 (d, 3H, J = 7 Hz), 1.98 (dd, 3H, J = 7 Hz, J = 1.2 Hz), 3.2-3.7 (m, 1H), 4.2 (dd, 1H, J = 11 Hz, J = 8 Hz) and 4.6 (dd, 1H, J = 11 Hz, J = 6 Hz) [a], 6.6 (dq, 1H, J = 16 Hz, J = 1.2 Hz) and 7.3 (dq, 1H, J = 16 Hz, J ≃ 7 Hz) [b]
3c	1.60 (d, 3H, J = 6 Hz), 2.03 (d, 3H, J = 1.2 Hz), 2.15 (d, 3H, J = 0.8 Hz), 2.9 (dd, 1H, J = 17 Hz, J = 10 Hz) and 3.2 (dd, 1H, J = 17 Hz, J = 5 Hz) [a], 4.6-5.0 (m, 1H); 6.52 (m, 1H)
3d	1.43 (d, 3H, J = 7 Hz), 2.05 (d, 3H, J = 1.2 Hz), 2.15 (d, 3H, J = 0.8 Hz), 3.2-3.7 (m, 1H), 4.2 (dd, 1H, J = 11 Hz, J = 8 Hz) and 4.6 (dd, 1H, J = 11 Hz, J = 6 Hz) [a], 6.51 (m, 1H).
3e	1.57 (s, 6H), 2.03 (d, 3H, J = 1.2 Hz), 2.16 (d, 3H, J = 0.8 Hz), 3.15 (s, 2H), 6.55 (m, 1H).

[a] AB part of ABX system, in first order treatment. [b] AB part of ABX_3 system, in first order treatment.

relaxing activity, *in vitro*, on the isolated guinea pig lung without anticholinergic of β_2-agonist effect (minimal inhibitory concentration: **3a** 50 μg/ml; aminophylline 100 μg/ml).

Acknowledgement.

The authors with to thank Societé LIPHA for the biological testing.

REFERENCES AND NOTES

[1] B. Chantegrel and S. Gelin, *Synthesis,* 315 (1981).

[2] B. Chantegrel, A. I. Nadi and S. Gelin, *Heterocycles,* **22**, 365 (1984).

[3] B. Chantegrel, A. I. Nadi and S. Gelin, *J. Heterocyclic Chem.*, **21**, 13 (1984).

[4] The *E* configuration of the oxime **2a** was assigned on the basis of the deshielding of one of the H-3 protons by the oxygen atom of the hydroxyimino group.

[5] The assignment of the carbon atoms was made on the basis of off-resonance decoupling and examination of the coupled spectra.

[6] J. Gainer, G. A. Howarth, W. Hoyle and S. M. Roberts, *Org. Magn. Reson.*, **8**, 226 (1976).

[7] A. L. Baumstark, D. R. Chrisope, R. A. Keel and D. W. Boykin, *J. Heterocyclic Chem.*, **17**, 1719 (1980).

[8] D. R. Chrisope, R. A. Keel, A. L. Baumstark and D. W. Boykin, *J. Heterocyclic Chem.*, **18**, 795 (1981).

[9] C. Deshayes, M. Chabannet and S. Gelin, *Synthesis,* 868 (1984).