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The title compounds were prepared from 3-alkenyl-1-phenyl-2-pyrazolin-5-one derivatives and α,β -unsaturated acyl chlorides as potential cardiotoxic agents.

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Our interest in the synthesis of potentially useful new therapeutic agents, has led us to prepare a series of 4-oxo-1-phenyl-5,6-dihydro-1*H*,4*H*-pyrano[2,3-*c*]pyrazole derivatives bearing an alkenyl substituent at the 3-position.

A previous paper from this laboratory has reported on the synthesis of 3-alkenyl-1-phenyl-2-pyrazolin-5-ones **1**, **3** and **4** and their *C*-acylation using magnesium ethylate as base and tetrahydrofuran as solvent [1]. This method has now been extended to the synthesis of the fused-pyrazoles **8**. Acylation of compounds **1-6** with α,β -unsaturated acyl chlorides afforded the intermediate 4-acyl derivatives **7**. When these compounds were heated to reflux in ethanolic hydrogen chloride the corresponding ring-closed compounds **8** were obtained in good yields. Spectral and ana-

lytical data for all the products described were consistent with the assigned structures (Table I and II).

Positive inotropic activity of these products was assessed with electrically stimulated isolated guinea pig left auricle preparation. Dopamine and sulmazole "Vardax" (Boehringer) were used as standard drugs. Of the derivatives tested, three compounds **8b,c** and **e** showed an inotropic activity at $10^{-5}M$. Compounds **8c** displayed an equipotent activity at $10^{-4}M$ as sulmazole.

Unfortunately, this compound was devoid of activity in dogs.

EXPERIMENTAL

Melting points were determined on a Kofler hot plate. Infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and DB spectrometers. The ¹H-nmr spectra were taken on a Bruker WP 80 spectrometer with respect to TMS. Elemental analyses were performed by Microanalytical laboratory, Centre National de la recherche scientifique, 69390 Vernaison, France.

Compounds **1**, **3**, **4** [1] and **6** [3] were prepared as previously described. Compounds **2** and **5** were synthesized according to the procedure described for **1**.

3-Isopropenyl-1-phenyl-2-pyrazolin-5-one (2).

This compound was prepared from ethyl 4-methyl-3-oxo-4-pentenoate [2] in a yield of 45% after column chromatography on silica gel using methylene chloride as eluent, mp 58° (ethanol); ir (chloroform): 1715 cm⁻¹ (C=O); uv (ethanol): λ max 259 nm (ϵ = 19000); ¹H-nmr (deuteriochloroform): δ 2.12 (s, 3H), 3.65 (s, 2H), 5.37 (s, 1H), 5.47 (m, 1H), 7.1-7.6 (m, 3H), 7.8-8.1 (m, 2H).

Anal. Calcd. for C₁₂H₁₂N₂O: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.87; H, 6.12; N, 13.84.

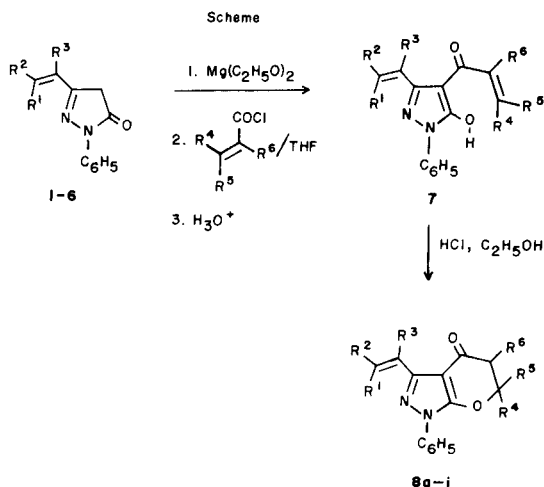
3-((*E,E*)-1,3-Pentadienyl)-1-phenyl-2-pyrazolin-5-one (5).

This compound was prepared from ethyl 3-oxo-(*E,E*)-4,6-octadienoate [4] in a yield of 51%, after recrystallization from acetonitrile, mp 125°; ir (chloroform): 1715 cm⁻¹ (C=O); uv (ethanol): λ max 284 nm (ϵ = 28800); ¹H-nmr (deuteriochloroform): δ 1.88 (d, 3H, J = 6 Hz), 3.58 (s, 2H), 5.8-6.8 (m, 4H), 7.1-7.6 (m, 3H), 7.8-8.1 (m, 2H).

Anal. Calcd. for C₁₄H₁₄N₂O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.33; H, 6.15; N, 12.45.

3-Alkenyl-4-oxo-1-phenyl-5,6-dihydro-1*H*,4*H*-pyrano[2,3-*c*]pyrazole Derivatives (8). General Procedure.

A mixture of compound **1**, **2**, **3**, **4**, **5** or **6** (0.02 mole), magnesium ethylate 2.28 g (0.02 mole) and dry toluene (100 ml) was stirred and



Starting pyrazolone	8	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
1	a	H	Me	H	H	Me	H
1	b	H	Me	H	H	H	Me
1	c	H	Me	H	Me	Me	H
1	d	H	Me	H	H	Me	Me
2	e	H	H	Me	H	Me	H
3	f	Me	Me	H	H	Me	H
4	g	H	Me	Me	H	Me	H
5	h	H	(<i>E</i>)-Me-CH=CH	H	H	Me	H
6	i	H	Ph	H	H	Me	H

Table I
Physical Data for Compounds **8**

Compound No.	Yield % [a]	Mp, °C Solvent	Molecular Formula	Analyses % (Calcd./Found)			IR (Chloroform) ν C=O cm^{-1}	UV (Ethanol) λ max nm (ϵ)
				C	H	N		
8a	70	104-105 [b]	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$	71.62 71.60	6.01 5.98	10.44 10.20	1680	250 (32600)
8b	70	140-142 [c]	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$	71.62 71.75	6.01 6.23	10.44 10.28	1680	250 (34900)
8c	50	131-132 [d]	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	72.32 72.47	6.43 6.44	9.92 9.99	1680	250 (32100)
8d <i>cis</i>	30	oil	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ [h]	72.32 72.21	6.43 6.42	9.92 9.95	1680	252 (35100)
8d <i>trans</i>	30	173-174 [e]					1680	250 (31600)
8e	60	82-83 [f]	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$	71.62 71.42	6.01 6.03	10.44 10.34	1680	248 (30400)
8f	60	146-147 [g]	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	72.32 72.62	6.43 6.13	9.92 9.76	1680	258 (32700)
8g	75	116-117 [b]	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	72.32 72.12	6.43 6.45	9.92 9.83	1675	250 (31800)
8h	75	137-138 [c]	$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$	73.45 73.26	6.16 6.27	9.52 9.35	1675	260 (35900) 290 (23100)
8i	75	139-140 [c]	$\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2$	76.34 76.34	5.49 5.68	8.48 8.34	1675	260 (30400) 300 (21100)

[a] Isolated yield by column chromatography. [b] Ethyl acetate/hexane 1:4. [c] Ethanol. [d] Ethyl acetate/hexane 2:3. [e] Ethyl acetate/hexane 1:1. [f] Hexane. [g] Ethyl acetate/hexane 1:2. [h] Analysis of the *cis-trans* isomeric mixture.

Table II

Proton Magnetic Resonance Parameters

Compound No.	Chemical (deuteriochloroform) [a]	Shift
8a	1.60 (d, 3H, J = 6 Hz), 1.93 (dd, 3H, J = 6 Hz, 2 Hz), 2.3-2.9 (m, 2H) [b], 4.91 (m, 1H), 6.67 (dq, 1H, J = 16 Hz, 2 Hz), 7.1-7.7 (m, 4H), 7.8-7.9 (m, 2H)	
8b	1.22 (d, 3H, J = 7 Hz), 1.92 (dd, 3H, J = 6 Hz, 2 Hz), 2.77 (m, 1H), 4.36 (dd, 1H, $J_{AB} = 11$ Hz, $J_{AX} = 10$ Hz), and 4.71 (dd, 1H, $J_{AB} = 11$ Hz, $J_{BX} = 5$ Hz) [c], 6.65 (dq, 1H, J = 16 Hz, 2 Hz), 7.1-7.7 (m, 4H), 7.7-7.9 (m, 2H)	
8c	1.60 (s, 6H), 1.96 (dd, 3H, J = 6 Hz, 2 Hz), 2.66 (s, 2H), 6.65 (dq, 1H, J = 16 Hz, 2 Hz), 7.0-7.7 (m, 4H), 7.7-7.8 (m, 2H)	
8d <i>cis</i>	1.18 (d, 3H, J = 7 Hz), 1.51 (d, 3H, J = 7 Hz), 1.95 (dd, 3H, J = 6 Hz, 2 Hz), 2.55 (dq, 1H, J = 3 Hz, 7 Hz), 4.92 (dq, 1H, J = 3 Hz, 7 Hz), 6.65 (dq, 1H, J = 16 Hz, 2 Hz), 7.0-7.7 (m, 4H), 7.7-8.0 (m, 2H)	
8d <i>trans</i>	1.25 (d, 3H, J = 7 Hz), 1.61 (d, 3H, J = 6 Hz), 1.95 (dd, 3H, J = 6 Hz, 2 Hz), 2.51 (dq, 1H, J = 10 Hz, 7 Hz), 4.56 (dq, 1H, J = 10 Hz, 6 Hz), 6.65 (dq, 1H, J = 16 Hz, 2 Hz), 7.0-7.7 (m, 4H), 7.7-8.0 (m, 2H)	
8e	1.61 (d, 3H, J = 6 Hz), 2.22 (s, 3H), 2.3-2.9 (m, 2H) [b], 4.91 (m, 1H), 5.55 (m, 1H), 6.67 (m, 1H), 7.1-7.7 (m, 3H), 7.7-7.8 (m, 2H)	
8f	1.60 (d, 3H, J = 6 Hz), 1.99 (s, 3H), 2.22 (s, 3H), 2.3-2.7 (m, 2H) [b], 4.90 (m, 1H), 6.69 (m, 1H), 7.1-7.7 (m, 2H)	
8g	1.57 (d, 3H, J = 6 Hz), 1.87 (dd, 3H, J = 7 Hz, 1 Hz), 2.12 (s, 3H), 2.3-2.9 (m, 2H) [b], 4.89 (m, 1H), 7.10 (m, 1H), 7.3-7.7 (m, 3H), 7.7-7.8 (m, 2H)	
8h	1.59 (d, 3H, J = 6 Hz), 1.84 (d, 3H, J = 6 Hz), 2.3-2.9 (m, 2H) [b], 4.9 (m, 1H), 5.7-6.8 (m, 3H), 7.2-8.0 (m, 6H)	
8i	1.60 (d, 3H, J = 6 Hz), 2.3-3.0 (m, 2H) [b], 4.95 (m, 1H),	

7.2-7.7 (m, 9H), 7.8-8.0 (m, 2H), 8.20 (d, 1H, J = 16 Hz)

[a] δ ppm from TMS. [b] ABX degenerate system $J_{AB} = 16$ Hz. [c] ABX system in first order treatment.

refluxed for 2 hours. The solvent was then evaporated *ion vacuo* and the residue was diluted with 100 ml of dry tetrahydrofuran. The mixture was then cooled to 0-5° and a solution of the α,β -unsaturated acyl chloride (0.02 mole) in tetrahydrofuran (25 ml) was added dropwise with efficient stirring. The cooling bath was removed and the residue was allowed to stand at room temperature for 3 hours or refluxed for 3 hours when 3,3-dimethyl and (*E*)-2,3-dimethyl acryloyl chlorides were used. The mixture was then poured onto cold 10% hydrochloric acid (300 ml) and extracted with chloroform (3 × 50 ml). The combined extracts were dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in ethanolic hydrogen chloride prepared from absolute ethanol (120 ml) and acetyl chloride (2 ml) and refluxed for 1 hour. After removal of ethanol, the crude compounds **8** were purified by column chromatography on silica gel (120 g) using methylene chloride as eluent. In the case of **8d**, two isomers were obtained. The *trans* isomer was first eluted and then the *cis*. Yields and physical data were summarized in the Tables I and II.

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REFERENCES AND NOTES

- [1] B. Chantegrel, A. I. Nadi and S. Gelin, *Heterocycles*, **20**, 1801 (1983).
- [2] P. Pollet and S. Gelin, *Synthesis*, 142 (1978).
- [3] J. Stanek and M. Holub, *Chem. Listy*, **47**, 404 (1953).
- [4] V. J. Lee, A. R. Branfman, T. R. Herrin and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **100**, 4225 (1978).