Synthesis of Some 4-Carboxy-3- and 5-(2-Hydroxyalkyl)pyrazole Lactone Derivatives

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The synthesis and biological activities of some 4-oxo-1-or-2-substituted 1*H*-or-2*H*-pyrano[4,3-*c*]pyrazole derivatives are described.

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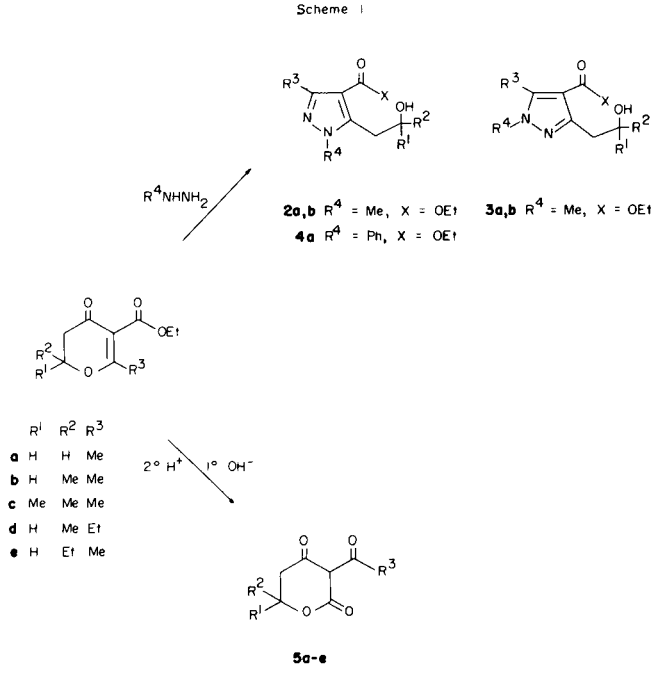
During our studies directed towards the synthesis of novel heterocycles of potential biological application, it was discovered that the 4-carboxy-5-(2-hydroxyethyl)-1,3-dimethylpyrazole lactone (**7a**) exhibited an analgesic activity. We report here the synthesis of a series of these fused pyrazoles in order to evaluate their activities.

Two different routes could be expected to lead to the required structure, one being on the initial formation of the pyrazole ring (Route 1), the other leaving the formation of the pyrazole ring for the last step (Route 2). We have previously described the synthesis of either the pyrazole derivatives (**2-4**) (1,2) or the 3-acyl-2,4-dioxo-3,4,5,6-tetrahydro-2*H*-pyranes (**5**) (3) from the appropriate and readily available 2,3-dihydro-4-pyrone derivatives (**1**) as starting material.

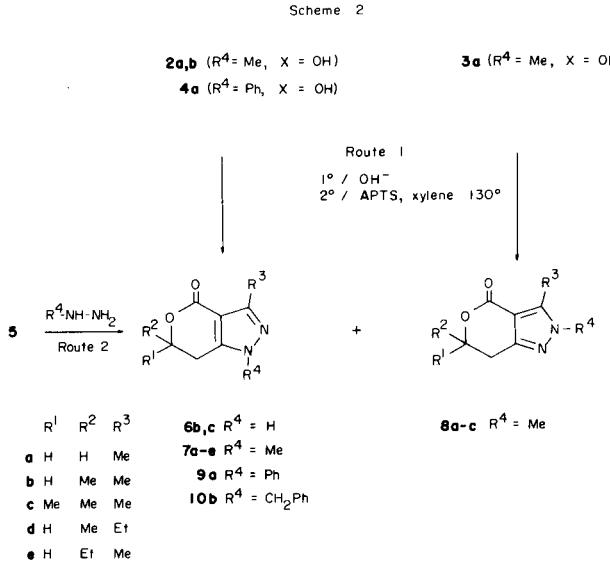
Scheme 1



Basic hydrolysis of the pyrazole esters (**2-4**) afforded the corresponding acids which were lactonized by heating with *p*-toluenesulfonic acid in boiling xylene (Route 1) to yield the corresponding pyrazole lactones (**7-9**). Structure determination of pyrazoles (**2-4**) was unambiguously established by means of ^{13}C nmr spectroscopy (1,2), the position of the *N*-substitution is therefore unequivocally determined in the compounds **7-9**.

Alternatively, reaction of compounds **5** with hydrazine hydrate, phenylhydrazine and benzylhydrazine, led to one product, respectively **6**, **9** and **10**; whereas, methylhydrazine gave an isomeric mixture of compounds **7** and **8** in the ratio of about 7:3 (Route 2). Structural confirmation rests upon comparison with compounds obtained from the Route 1.

Scheme 2



In principle, compounds **5** can react with nucleophilic reagents at either the C-4 position or at the carbonyl of the acyl chain. In addition, there are two nucleophilic positions in the alkylahydrazines. Our results imply that the initial attack occurs exclusively or preferentially (methylhydrazine) at the carbonyl of the acyl chain from the unsubstituted nitrogen of the alkylhydrazines. These findings are in agreement with the preferred orientation in the reaction of nucleophiles onto cyclic tricarbonylic substrates (5). The route 2 constitutes the most suitable way for the synthesis of the 4-carboxy-5-(2-hydroxyalkyl)-pyrazole lactone derivatives. It requires only two easy steps from the 2,3-dihydro-4-pyrone derivatives (**1**).

The pyrazole lactones were examined for antinflammatory and analgesic activity. The results of preliminary screening (Table 1) showed that only the 1-methyl-3,7-di-

substituted compounds possessed low activity, the other compounds were devoid of activity. Replacement of the 3-methyl group in **7b** by an ethyl group, **7d**, resulted in a relative increase in activity. Further studies directed towards the synthesis of various 3-substituted-1,3-dimethylpyrazole lactone derivatives are in progress.

Table 1

Pharmacological Activities
MED Values (a)

Compound No.	Test: Antiinflammatory Activity	Analgesic Activity	
	Carrageenan anti-oedema p.o. (rats)	Narcotic Tail flick s.c. (mice)	Non-narcotic Joint-pain/vocalization, s.c. (rats)
7a	200 (b)		200 (d)
7b	100 (b)	100 (c)	100 (e)
7d		50 (c)	100 (e)
7e		200 (c)	200 (d)

(a) Minimal effective dose in mg/kg; reference drug ED_{100}. (b) Aspirin 200 mg/kg/p.o. (c) Propoxyphene 200 mg/kg/s.c. (d) Phenylbutazone 200 mg/kg/s.c. (e) Ibuprofene 100 mg/kg/s.c.

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus and are uncorrected. The infrared spectra were recorded on a Beckman acculab 2 spectrometer in potassium bromide. The ultraviolet spectra were obtained on a Beckman DB spectrometer in ethanol. The proton nmr spectra were recorded using a Brucker WP 80 spectrometer with respect to TMS. Elemental analyses were performed by Microanalytical laboratory, Centre National de la recherche scientifique, 69390 Vernaison, France. Compounds **2**, **3** (1), **4** (2) and **5a-d** (3) were prepared as previously described.

3-Acetyl-6-ethyl-2,4-dioxo-3,4,5,6-tetrahydro-2*H*-pyrane (**5e**).

This compound was obtained in 42% yield in two steps from ethyl acetoacetate and 2-pentenoyl chloride by a method identical with the described procedure for **5b** (3), mp 54° (hexane); uv (ethanol): λ max 271 (ε, 7400); ir (potassium bromide): 1700 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.07 (3H, t, J = 7 Hz), 1.5-2.1 (2H, m), 2.5-2.8 (2H, m), 2.64 (3H, s), 4.37 (1H, m), enolic proton is not observed.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.55; H, 6.43.

1-Substituted-4-carboxy-5-(2-hydroxyalkyl)pyrazole Lactones (**7a,b** and **9a**). Route 1.

A mixture of pyrazole-ester (0.01 mole, X = OEt, **2a,b** or **4a**) and 2 *N* potassium hydroxide (20 ml) was allowed to stand overnight at room temperature. After extraction with ethyl ether, the aqueous layer was acidified with concentrated hydrochloric acid. The crude pyrazole acid (X = OH, **2a,b** or **4a**) was filtered; it was pure enough for the next step as shown by ^1H nmr. The pyrazole acid and *p*-toluenesulfonic acid (0.01 g) were refluxed for 4 hours in xylene (50 ml) with a Dean and Stark apparatus. The xylene was rotoevaporated and the residue dissolved in chloroform. The solution was washed with 5% sodium hydrogencarbonate, water and then dried. After evaporation of the solvent, ethyl ether, (10 ml) was added to the solid residue. The pyrazole lactone was collected by filtration. Yields are: **7a** (63%), **7b** (79%), **9a** (79%). These compounds were identical to those obtained from the Route 2.

2-Substituted-4-carboxy-5-(2-hydroxyalkyl)pyrazole Lactones (**8a,b**). Route 1.

Table 2

Physical Data for Compounds **6-10**

Compound No.	Yield % (a)	Mp (°C) Solvent	Molecular Formula	Analyses % Calcd./Found C	H	N	UV λ max nm (ε	IR (cm^{-1}) ν CO
6b	84	145-146 ethyl acetate	$C_8H_{10}N_2O_2$	57.82 57.85	6.07 6.07	16.89 16.59	232 (7500)	1700
6c	83	144-146 (b) ethyl acetate	$C_9H_{12}N_2O_2$	59.98 59.80	6.71 6.84	15.55 15.45	230 (8400)	1680
7a	35	98-99 ethyl acetate	$C_8H_{10}N_2O_2$ (c)	57.82 57.78	6.07 6.07	16.86 16.73	234 (7500)	1725
7b	35	125-126 ethyl acetate	$C_9H_{12}N_2O_2$ (c)	59.98 59.71	6.71 6.48	15.55 15.65	234 (7300)	1720
7c	32	88-89 ethyl acetate	$C_{10}H_{14}N_2O_2$ (c)	61.83 61.70	7.27 7.21	14.42 14.37	233 (8500)	1710
7d	25	83-84 ether	$C_{10}H_{14}N_2O_2$	61.83 62.11	7.27 7.18	14.42 14.54	233 (8500)	1720
7e	15	91-92 ether	$C_{10}H_{14}N_2O_2$	61.83 61.90	7.27 7.18	14.42 14.57	233 (8500)	1715
8a	12	102-103 (d)	$C_8H_{10}N_2O_2$ (c)	57.82 57.78	6.07 6.07	16.86 16.73	236 (7000)	1740
8b	13	142-143 (d)	$C_9H_{12}N_2O_2$ (c)	59.98 59.71	6.71 6.48	15.55 15.65	236 (7600)	1720
8c	13	104-106 (d)	$C_{10}H_{14}N_2O_2$ (c)	61.83 61.70	7.27 7.21	14.42 14.37	234 (8500)	1715
9a	68	180-181 ethanol	$C_{13}H_{12}N_2O_2$	68.41 67.93	5.30 5.39	12.27 12.25	225 (7400) sh 254 (13400)	1730
10b	69	102-103 ethyl acetate	$C_{15}H_{16}N_2O_2$	70.29 70.47	6.29 6.32	10.93 10.98	233 (10600)	1730

(a) Route 2. (b) Lit mp 144-146° (6). (c) Analysis of mixture **7a + 8a**, **7b + 8b** or **7c + 8c**. (d) Purified by column chromatography.

Table 3

Proton Magnetic Resonance Parameters of Compounds **6-10** in Deuteriochloroform (δ, ppm), (J, Hz)

Compound No.	
6b	1.58 (d, 3H, J = 6.5), 2.65 (s, 3H), 2.87-3.27 (m, 2H), 4.58-5.17 (m, 1H), 12.43 (broad, 1H).
7a	2.47 (s, 3H), 3.05 (t, 2H, J = 6), 3.88 (s, 3H), 4.63 (t, 2H, J = 6).
7b	1.58 (d, 3H, J = 6.5), 2.48 (s, 3H), 2.83-3.31 (m, 2H), 3.86 (s, 3H), 4.52-5.10 (m, 1H).
7c	1.53 (s, 6H), 2.49 (s, 3H), 3.02 (s, 2H), 3.88 (s, 3H).
7d	1.27 (t, 3H, J = 7), 1.55 (d, 3H, J = 7), 2.5-3.1 (m, 4H), 3.79 (s, 3H), 4.70 (m, 1H).
7e	1.08 (t, 3H, J = 7), 1.6-2.1 (m, 2H), 2.45 (s, 3H), 2.7-3.1 (m, 2H), 3.80 (s, 3H), 4.47 (m, 1H).
8a	2.58 (s, 3H), 2.99 (t, 2H, J = 6), 3.90 (s, 3H), 4.62 (t, 2H, J = 6).
8b	1.56 (d, 3H, J = 6.5), 2.60 (s, 3H), 2.78-3.18 (m, 2H), 3.90 (s, 3H), 4.53-5.20 (m, 1H).
8c	1.50 (s, 6H), 2.63 (s, 3H), 2.98 (s, 2H), 3.92 (s, 3H).
9a	2.58 (s, 3H), 3.22 (t, 2H, J = 6), 4.62 (t, 2H, J = 6), 7.68 (s, 5H).
10b	1.44 (d, 3H, J = 7.5), 2.45 (s, 3H), 2.4-3.1 (m, 2H), 4.3-4.9 (m, 1H), 5.23 (s, 2H), 7.0-7.5 (m, 5H).

A mixture of isomeric pyrazole esters (**2a,b**) and (**3a,b**) (X = OEt) (1) in the ratio of about 1:2, by use of the same procedure described above, except that the acids were continuously extracted with ethyl ether for 24 hours, gave a material which was shown by ^{1}H nmr to consist of the two isomeric pyrazole lactones (**7**) and (**8**) in the ratio of about 1:2, whose spectral data were found to be identical with those described above. Pure compounds **8** were separated by column chromatography (see Route 2).

4-Carboxy-5-(2-hydroxyalkyl)pyrazole Lactones (**6b,c**).

Hydrazine hydrate (1.1 g, 0.022 mole) and acetic acid (1 ml) were added to a solution of **5b** or **5c** (0.020 mole) in ethanol (50 ml). The mixture was refluxed for 3 hours and the solvent was removed under reduced pressure. The residual product was recrystallized from ethyl acetate to afford the title compounds.

N-Substituted-4-carboxy-5-(2-hydroxyalkyl)pyrazole Lactones (**7a-e, 8a-c, 9a, 10b**). General Procedure. Route 2.

A mixture of compound **5** (0.020 mole) and alkylhydrazine (methylhyrazine, phenylhydrazine or benzylhydrazine) (0.021 mole) and ethanol (50 ml) was refluxed for two hours and then the reaction mixture was treated as described below.

Work-up Procedure for Products **7a-e**.

The solvent was evaporated to dryness to give a 7:3 mixture of **7/8**, respectively, as determined by ^{1}H nmr analysis. Pure compounds **7a-e** were obtained by two recrystallizations of the crude mixture from a suitable solvent (Table 2).

Work-up Procedure for Products **8a-c**.

The yields of crude products **7** + **8** were **a**, 63%, **b**, 76%, **c** 70%. The crude mixture (1.5 g) was column chromatographed on silica gel (30 g), eluting with ethyl ether. The compounds **8** were first eluted **8a**, 0.3 g (12%), **8b**, 0.25 g (13%), **8c**, 0.29 g (13%) and then the compounds **7**: **7a**, 0.84 g (35%), **7b**, 0.7 g (35%), **7c**, 0.69 g (32%).

Work-up Procedure for Product **9a**.

The reaction mixture was cooled and the resulting precipitate was collected by filtration and washed with ether to give **9a**.

Work-up Procedure for Product **10b**.

Ethanol was removed under reduced pressure and the residue was dissolved in ethyl acetate (3 ml). After one day, the solid that separated was collected and washed with ether to give **10b**.

The yields and physical data are given in Tables 2 and 3.

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