Synthesis of some Isomeric 4-Ethoxycarbonyl-3- and 5-(1- and 2-Hydroxyalkyl)-1,3- and 1,5-Dimethylpyrazoles from 3-(2*H*)Furanones and 2,3-Dihydro-4-pyrones

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The title compounds were prepared by reaction of 3-(2*H*)furanones and 2,3-dihydro-4-pyrones with methylhydrazine or alternatively by methylation of the corresponding *N*-unsubstituted pyrazoles. ^{13}C and ^{1}H nmr were used to assign the isomeric 3-methyl or 5-methyl structures.

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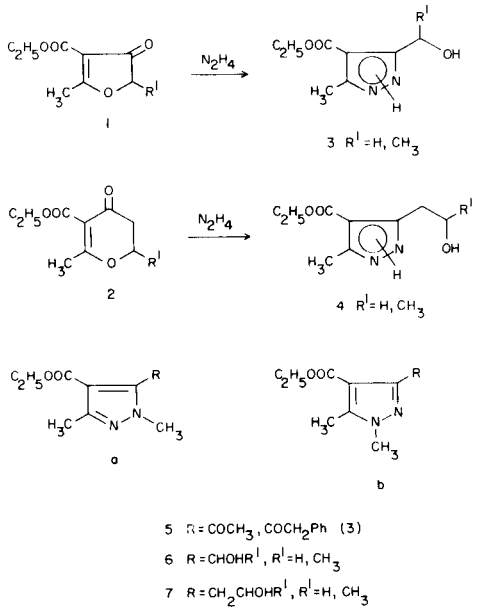
We recently reported the reaction of hydrazine hydrate with 3-(2*H*)furanones **1** (1) and with 2,3-dihydro-4-pyrones **2** (2), leading to the corresponding 3(or 5)-(1-hydroxyalkyl) and 3(or 5)-(2-hydroxyalkyl)-4-ethoxycarbonylpyrazoles **3** and **4**, respectively. We now report work on the reaction of the compounds **1** and **2** with methylhydrazine and on the methylation reaction of the pyrazoles **3** and **4**, in order to extend our previous findings concerning the conversion and the structure determination of the isomeric *N*-alkyl-3- and 5-acylpyrazoles **5a** and **5b** (3) to the isomeric *N*-alkyl-3- and 5-(1- and 2-hydroxyalkyl)-5- and 3-methylpyrazoles **6** and **7a,b**.

Scheme I



Treatment of compounds **1** and **2** with methylhydrazine resulted in the formation of an isomeric mixture of the corresponding pyrazoles **a** and **b**. The substituted nitrogen atom in methylhydrazine is the better nucleophile, but it is also the more hindered nitrogen. Our results listed in Table I show that the reaction products **7** obtained from the dihydropyrones **2** are principally derived from initial nucleophilic attack by the unsubstituted nitrogen of the methylhydrazine. This is probably a consequence of the more important 2,6 interference in the sofa dihydropyrone ring (4) as compared to the 2,5-interference in the dihydrofuranone ring. The evidence for the configuration of the products will be discussed below.

Table I

Action of Methylhydrazine with Compounds **1** and **2**

Compound No.	R^1	% a (a)	% b
6	H	68	32
6	CH_3	62	38
7	H	92	8
7	CH_3	90	10

(a) Determined by ^{1}H nmr spectroscopy.

Methylation of the pyrazoles **3** and **4** may be carried out in a conventional way with potassium carbonate and methyl iodide in a variety of solvents. Best results were obtained in all cases with dimethoxyethane as the solvent (with dimethylsulfoxide, the reaction products could not be readily extracted from the reaction mixture). We also found that the pyrazoles **3** can readily be methylated in cyclohexanone solution, whereas the pyrazoles **4** afforded 4,5-dihydro-7*H*-pyrazolo[1,5-*c*]-1,3-oxazine derivatives (5). Table II records the **a/b** product ratios for these methylation reactions. It is difficult to come to an unambiguous conclusion concerning the effects of the 3(or 5)- alkyl groups on the orientation of *N*-methylation. However, the difference observed from **3**, R^1 = H to **3** R^1 = CH_3 could be due to a steric effect.

The pure isomeric pyrazole series **a** and **b** were obtained by recrystallization or column chromatography. The structural assignments of the isomeric 3-methyl or 5-methyl pyrazoles **a** or **b**, respectively, are principally based on ^{13}C

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Table II

Methylation of Pyrazoles **3** and **4**

Compound No.	R^1	Solvent	% **a** (a)	% **b**
6	H	Dimethoxyethane	39	61
		Cyclohexanone	29	71
6	CH_3	Dimethoxyethane	28	72
		Cyclohexanone	20	80
7	H	Dimethoxyethane	37	63
7	CH_3	Dimethoxyethane	39	61

(a) The ratios were determined by nmr analysis of the reaction products.

nmr spectroscopy of compounds **6** and **7** (R^1 = H), as model compounds. The coupled spectrum of **6** (R^1 = H) **a** and **b**, provided a straightforward assignment of the carbon resonances of these heterocycles. The *N*-methylpyrazoles exhibit 3-bond ^{13}C-H coupling, identifying which is C-3 and which C-5. In the coupled spectrum of **6a**, the signal at 146.5 ppm was assigned to C-5: quadruplet, ^3J = 6 Hz and triplet ^2J = 6 Hz. The C-3 resonance at 149.8 ppm appears as a quadruplet ^2J = 6.6 Hz. In the coupled spectrum of **6b**, the triplet at 153.3 ppm (^2J = 4 Hz) was assigned to the C-3 resonance and the line at 144.1 ppm was attributed to the C-5 carbon resonance:

Table III

Carbon-13 Chemical Shifts for Isomeric 1,3- and 1,5-Dimethylpyrazoles (Deuteriochloroform) δ (ppm)

Compound No.	C-3	C-4	C-5	R (3)	R (5)	NCH_3	CO_2	CH_2	CH_3
6a	149.8	109.9	146.5	CH_3: 14.1	CH_2OH: 54.3	36.4	164.9	60.2	14.3
7a	149.9	109.4	145.5	CH_3: 14.1	CH_2: 28.6 CH_2OH: 58.9	36.2	164.5	61.2	14.3
6b	153.3	108.9	144.1	CH_2OH: 58.7	CH_3: 11.2	36.1	164.7	60.3	14.3
7b	151.5	109.3	143.8	CH_2: 31.1 CH_2OH: 59.6	CH_3: 11.2	36.0	164.2	61.4	14.3

Table IV

Change in Carbon-13 Chemical Shifts for an Isomeric Pair of Pyrazoles (a)

Compounds Compared	C-3	C-4	C-5	CH_3	CH_2-$(CH_2)_n$OH	N-CH_3
6a-6b R^1 = H	5.7	1	−6.8	2.9	−4.4 (n = 0)	0.3
7a-7b R^1 = H	6.1	0.1	−6.0	2.9	−2.5 (n = 1)	0.2

(a) $\Delta\delta$ = δC **a** - δC **b** as compared to the chemical shifts observed for the corresponding positions of the 3-methyl isomer **a**.

Table V

Pertinent ^1H Nmr Spectral Data (Deuteriochloroform) of Pyrazoles **6** and **7** (δ ppm)

Compound No.	R (3)	R (5)	N-CH_3
6a	CH_3, 2.44 (s)	CH_2OH, 4.85 (s)	3.88 (s)
6a	CH_3, 2.42 (s)	$CHOHCH_3$, 5.28 (q, J = 6.5 Hz)	3.88 (s)
7a	CH_3, 2.41 (s)	CH_2CH_2OH, 3.27 (t, J = 6 Hz)	3.88 (s)
7a	CH_3, 2.40 (s)	$CH_2CHOHCH_3$, 2.68-3.62 (m) (a)	3.87 (s)
6b	CH_2OH, 4.82 (s)	CH_3, 2.55 (s)	3.84 (s)
6b	$CHOHCH_3$, 5.18 (q, J = 6.5 Hz)	CH_3, 2.53 (s)	3.82 (s)
7b	CH_2CH_2OH, 3.20 (t, J = 6 Hz)	CH_3, 2.55 (s)	3.83 (s)
7b	$CH_2CHOHCH_3$ (a)	CH_3, 2.50 (s)	3.79 (s)

(a) ABX pattern, X protons are obscured by the methylene protons of the ethoxycarbonyl group.

Table VI

Physical, Analytical and Spectroscopic Data for Compounds **6** and **7**

Compound No.	R'	Procedure (a)	Yield %	M.p. °C (b)	Empirical Formula	Elemental Analysis Calcd. % C	H	N	Found % C	H	N	Uv in Ethanol λ nm (ε)	Ir (cm^{-1}) (Chloroform)
6a	H	A	45	98 (c)	$C_9H_{14}N_2O_3$	54.53	7.12	14.13	54.55	7.14	14.36	235 (8500)	3430 1690
6b	H	B	55	37 (d)					54.56	7.00	14.27	232 (8200)	3450 1690
6a	CH_3	A	45	107 (c)	$C_{10}H_{16}N_2O_3$	56.59	7.60	13.20	56.65	7.65	13.15	234 (9400)	3380 1690
6b	CH_3	B	60	64 (e)					56.48	7.55	13.39	234 (8900)	3440 1690
7a	H	A	80	80 (f)	$C_{10}H_{16}N_2O_3$	56.59	7.60	13.20	56.30	7.70	13.30 (h)	234 (8900)	3450 1705
7b	H	B	14	85 (f)								233 (8200)	3450 1705
7a	CH_3	A	62	77 (f)	$C_{11}H_{18}N_2O_3$	58.39	8.02	12.38	58.31	7.99	12.33 (h)	233 (9500)	3430 1705
7b	CH_3	(g)											

(a) A: purified from the reaction mixture of **1** or **2** and methylhydrazine; B: purified from the alkylation reaction of **3** or **4**, as described in Experimental. (b) Recrystallization solvent: c, ether; d, hexane/ethyl acetate (4:1); e, hexane; f, hexane/ethyl acetate (9:1). (g) Purification of this compound was unsuccessful. (h) Analysis of Mixture **7a** + **7b**.

quadruplet, ^3J = 6 Hz and quadruplet, ^2J = 6 Hz. Based on this first ^{13}C nmr spectral evidence, the correctness that the C-3 methyl signal is shifted to lower field than the C-5 methyl signal was of immediate value in assigning the structure in an isomeric pair of pyrazoles, and this supported our earlier assertion (3) concerning the structural assignment of acylpyrazoles **5a** and **5b**. The methylene carbon chemical shifts in the C-3 position are also deshielded as compared to the C-5 position. The chemical shifts of compounds **6** and **7** (R^1 = H) are presented in Table III. The carbons 3,4 and 5 in series **a** must correspond to carbons 5,4 and 3, respectively, in series **b**. The comparison of the chemical shifts from two *N*-methyl isomers observed for the corresponding position in the 3-methyl series as reference compound are given in Table IV.

An analysis of the ^1H nmr spectra of the pair of the isomeric pyrazoles (Table V) shows that the most interesting difference for these compounds is that the chemical values for the 3 or 5 methyl protons are deshielded in going from the 3- to the 5-methyl isomer. A deshielding shift is also observed for the methylene and the methine protons in going from the 3-hydroxyalkyl to the 5-hydroxyalkyl isomer. These observations are in agreement with previous findings concerning the resonance interaction of electron withdrawing substituents in the 4 or 5 position of the pyrazole ring (6,7).

EXPERIMENTAL

Melting points were determined on a Kofler hot plate and are uncorrected. Infrared and ultraviolet spectra were obtained with a Beckman Model Acculab 2 and DB spectrophotometers. ^1H-nmr spectra were taken on a Varian A-60 instrument; ^{13}C-nmr spectra were obtained with a Varian XL-100-12FT. The chemical shifts reported are in parts per million form internal TMS. Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

Compounds **1** (1), **2** (8,9), **3** (1) and **4** (2) were prepared as previously described.

Reaction of Compounds **1** and **2** with Methylhydrazine.

Procedure A. Preparation of Pyrazole Series **a**.

To a solution of compound **1** or **2** (10 mmoles) in ethanol (10 ml.), was added methylhydrazine (0.92 g., 20 mmoles). The reaction mixture was allowed to stand at room temperature for 2 hours and the ethanol was evaporated on the rotary evaporator. The crude products were analyzed by ^1H-nmr. The pure pyrazole series **a** were obtained as described below.

4-Ethoxycarbonyl-5-(1-hydroxymethyl)-1,3-dimethylpyrazole (**6a**, R^1 = H).

The residual mixture was chromatographed on silica gel (30 g.). Elution with ether (140-210 ml.) gave the pyrazole **a**. Isomer **b** was then eluted.

4-Ethoxycarbonyl-5-(1-hydroxyethyl)-1,3-dimethylpyrazole (**6a**, R^1 = CH_3).

The residual mixture was chromatographed on silica gel (30 g.). Elution with ether (100 to 160 ml.) gave first the pure pyrazole **a**.

4-Ethoxycarbonyl-5-(2-hydroxyethyl)-1,3-dimethylpyrazole (**7a**, R^1 = H).

The residual solid was recrystallized from hexane/ethyl acetate (9:1).

4-Ethoxycarbonyl-5-(2-hydroxypropyl)-1,3-dimethylpyrazole (**7a**, $R^1 = CH_3$).

The residue was taken up with chloroform (50 ml.). The organic extract was washed with 1*N* hydrochloric acid then with water and dried. The solvent was removed *in vacuo*. The residual solid was recrystallized from hexane/ethyl acetate (9:1).

Methylation of Pyrazoles **3** and **4**.

Procedure B. Preparation of Pyrazole Series **b**.

To a stirred solution of pyrazole **3** or **4** (10 mmoles) in dimethoxyethane (10 ml.) or cyclohexanone (10 ml.) in the case of compounds **3**, was added potassium carbonate (1.5 g., 11 mmoles) and methyl iodide (6.8 g., 50 mmoles). The mixture was then heated under reflux for 4 hours. The precipitate was filtered off and then the solvent was removed *in vacuo*. The residue was analyzed by ^{1}H-nmr. The crude products were purified as described below.

4-Ethoxycarbonyl-3-(1-hydroxymethyl)-1,5-dimethylpyrazole (**6b**, $R^1 = H$).

The residual mixture (from cyclohexanone as solvent) was chromatographed on silica gel (30 g.). Elution with ether (140-210 ml.) gave the pyrazole **a** and then (260 to 430 ml.) the pyrazole **b**.

4-Ethoxycarbonyl-3-(1-hydroxyethyl)-1,5-dimethylpyrazole (**6b**, $R^1 = CH_3$).

The residual solid was chromatographed on silica gel (30 g.). Elution with ether (100 to 160 ml.) afforded the isomer **a**, then (210 to 410 ml.), the pure isomer **b**.

4-Ethoxycarbonyl-3-(2-hydroxyethyl)-1,5-dimethylpyrazole (**7b**, $R^1 = H$).

The residual solid was treated three times by 10 ml. of a mixture hexane/ether (1:1) for 1 hour with stirring at room temperature. The filtration of the insoluble precipitate furnished the pure product.

Melting points, yields and elemental analyses are reported in Table VI.

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