Synthesis of 5-Substituted 1-Aryl-1*H*-pyrazole-4-acetonitriles, 4-Methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles and Pharmacologically Active 1-Aryl-1*H*-pyrazole-4-acetic Acids

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Lithium aluminum hydride reduction of 5-substituted or unsubstituted ethyl or methyl 1-aryl-1*H*-pyrazole-4-carboxylates gave, generally in excellent yields, 5-substituted or unsubstituted 1-aryl-1*H*-pyrazole-4-methanols which afforded the corresponding 1-aryl-4-(bromomethyl)-1*H*-pyrazoles with hydrobromic acid in acetic acid solution. These crude intermediates gave by reaction with potassium cyanide in dimethylsulfoxide solution 1-aryl-1*H*-pyrazole-4-acetonitriles only in the case of 5-unsubstituted compounds, otherwise mixtures of 5-substituted 1-aryl-1*H*-pyrazole-4-acetonitriles and 4-methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles were generally obtained. Acetonitriles **IIIa,b,i,l** gave in excellent yields the corresponding 1-aryl-1*H*-pyrazole-4-acetic acids **Va,b,i,l** by alkaline hydrolysis. Compounds **Vb,i,l** showed in the writhing test appreciable analgesic properties, associated with low acute toxicity; moreover, compound **VI** exhibited a statistically significant antiinflammatory activity in the carrageenan-induced edema assay.

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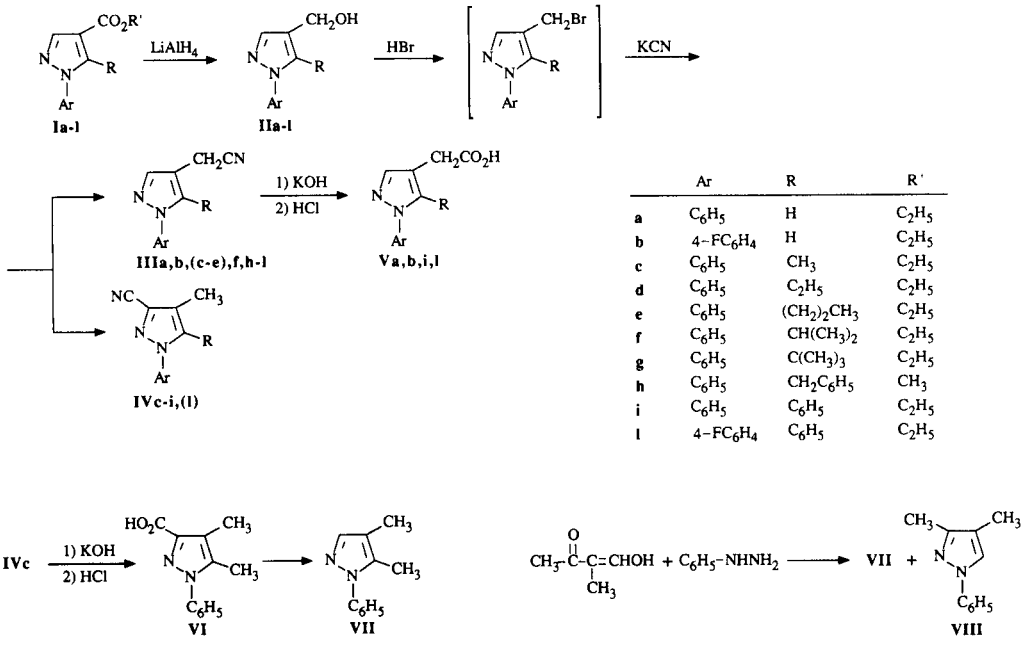
In a previous paper [1] we reported a convenient synthesis of ethyl or methyl 5-substituted 1-phenyl-1*H*-pyrazole-4-carboxylates **I** by reaction of ethyl or methyl 2-dimethylaminomethylene-3-oxoalkanoates with phenylhydrazine. Successively, this reaction was extended *inter alia* to methyl 4-methoxy-2-dimethylaminomethylene-3-oxobutanoate to obtain methyl 5-methoxymethyl-1-phenyl-1*H*-pyrazole-4-carboxylate, which was converted in a five steps sequence to 1-phenyl-1*H*-pyrazole-5-acetic acid, showing strong antiinflammatory, analgesic and antipyretic activities in rats and mice [2].

Since we are interested to the synthesis of other 1-aryl-1*H*-pyrazoleacetic acids in order to study their pharmacological effects, we sought to employ 1-aryl-1*H*-pyrazole-4-carboxylates **I** to obtain 5-substituted or unsubstituted 1-aryl-1*H*-pyrazole-4-acetic acids **V**, few examples of which are known [3-5] (Scheme 1).

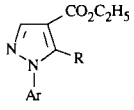
Scheme 1



	Ar	R	R'
a	C_6H_5	H	C_2H_5
b	4-FC_6H_4	H	C_2H_5
c	C_6H_5	CH_3	C_2H_5
d	C_6H_5	C_2H_5	C_2H_5
e	C_6H_5	$(CH_2)_2CH_3$	C_2H_5
f	C_6H_5	$CH(CH_3)_2$	C_2H_5
g	C_6H_5	$C(CH_3)_3$	C_2H_5
h	C_6H_5	$CH_2C_6H_5$	CH_3
i	C_6H_5	C_6H_5	C_2H_5
l	4-FC_6H_4	C_6H_5	C_2H_5

Table I

Ethyl 1-Aryl-1*H*-pyrazole-4-carboxylates **Ia,b,l**



Formula Number	R	Ar	Yield %	Mp °C	Molecular Formula	Analyses % Calcd. / Found C	H	N
Ia	H	C_6H_5	59	96-97 [a][b]	$C_{12}H_{12}N_2O_2$	66.65 66.38	5.59 5.54	12.95 12.86
Ib	H	4-FC_6H_4	78	124-125 [a]	$C_{12}H_{11}FN_2O_2$	61.53 61.48	4.73 4.75	11.96 11.88
Il	C_6H_5	4-FC_6H_4	90	71-72 and 78-79 [c]	$C_{18}H_{15}FN_2O_2$	69.67 69.55	4.87 4.87	9.03 9.04

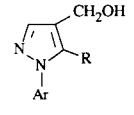
IR and ^1H NMR Spectral Data

	IR, cm^{-1}	^1H NMR, δ
Ia	1710, 1600, 1557, 1505	1.35 (t, J = 7, 3H, CH_3), 4.34 (q, J = 7, 2H, CH_2), 7.3-7.9 (m, 5H, C_6H_5), 8.12 (s, 1H, H-3), 8.42 (s, 1H, H-5)
Ib	1712, 1610, 1556, 1514	1.36 (t, J = 6.5, 3H, CH_3), 4.35 (q, J = 6.5, 2H, CH_2), 6.9-7.4 (m, 2H, ar 2,6), 7.5-7.9 (m, 2H, ar 3,5), 8.11 (s, 1H, H-3), 8.38 (s, 1H, H-5)
Il	1703, 1606, 1550, 1508	1.22 (t, J = 7, 3H, CH_3), 4.23 (q, J = 7, 2H, CH_2), 6.6-7.6 (m, 9H, C_6H_5 + C_6H_4), 8.21 (s, 1H, H-3)

[a] From 95% ethanol. [b] Reference [10], mp 96-97 °C. [c] From petroleum ether (bp 40-70 °C).

Table II

1-Aryl-4-(hydroxymethyl)-1*H*-pyrazoles **IIa-l**



Formula Number	R	Ar	Yield %	Mp °C or bp °C / mm	Molecular Formula	Analyses % Calcd. / Found C	H	N
IIa	H	C_6H_5	94	61-62 [a][c]	$C_{10}H_{10}N_2O$	68.95 69.16	5.79 5.81	16.08 16.28
IIb	H	4-FC_6H_4	96	85-86 [b]	$C_{10}H_9FN_2O$	62.49 62.60	4.72 4.73	14.58 14.48
IIc	CH_3	C_6H_5	89	88-89 [a]	$C_{11}H_{12}N_2O$	70.19 70.14	6.43 6.38	14.88 14.78
IId	CH_2CH_3	C_6H_5	89	66-68 [a]	$C_{12}H_{14}N_2O$	71.26 71.03	6.98 6.98	13.85 13.67
IIe	$(CH_2)_2CH_3$	C_6H_5	93	150-153 / 0.4	$C_{13}H_{16}N_2O$	72.19 71.80	7.46 7.56	12.95 13.08
IIf	$CH(CH_3)_2$	C_6H_5	91	63-65 [b]	$C_{13}H_{16}N_2O$	72.19 72.28	7.46 7.56	12.95 12.94
IIg	$C(CH_3)_3$	C_6H_5	91	159-161 [a]	$C_{14}H_{18}N_2O$	73.01 73.23	7.88 7.96	12.16 12.02
IIh	$CH_2C_6H_5$	C_6H_5	88	200-205 / 0.4	$C_{17}H_{16}N_2O$	77.25 76.96	6.10 6.11	10.60 10.78
IIi	C_6H_5	C_6H_5	52	149-151 [a]	$C_{16}H_{14}N_2O$	76.78 76.73	5.64 5.63	11.19 11.16
III	C_6H_5	4-FC_6H_4	96	116-117 [b]	$C_{16}H_{13}FN_2O$	71.63 71.43	4.88 4.90	10.44 10.40

[a] From diethyl ether. [b] From diethyl ether-petroleum ether 1:1. [c] Reference [11], mp 60.5-61 °C.

Table III

IR and ^1H NMR Spectral Data of Compounds **IIa-l**

Compound	IR, cm^{-1}	^1H NMR, δ
IIa	3605, 3370, 1600, 1570, 1500, 1463, 1402	2.71 (t, J = 5, 1H, OH; disappears with deuterium oxide), 4.62 (d, J = 5, 2H, CH_2; becomes s with deuterium oxide), 7.2-7.8 (m, 6H, C_6H_5 + H-3), 7.88 (s, 1H, H-5)
IIb	3605, 3390, 1603, 1568, 1512, 1402	2.32 (t, J = 5, 1H, OH; disappears with deuterium oxide), 4.65 (d, J = 5, 2H, CH_2; becomes s with deuterium oxide), 6.9-7.8 (m, 5H, C_6H_4 + H-4), 7.85 (s, 1H, H-3)
IIc	3605, 3360, 1598, 1570, 1498, 1450, 1388	2.29 (s, 3H, CH_3), 2.66 (br s, 1H, OH; disappears with deuterium oxide), 4.53 (br s, 2H, CH_2; becomes s with deuterium oxide), 7.44 (s, 5H, C_6H_5), 7.57 (s, 1H, H-3)
IId	3605, 3350, 1598, 1565, 1498, 1475, 1453, 1393	1.06 (t, J = 7, 3H, CH_3), 2.45-3.0 (m, 3H, CH_2Me + OH; becomes q with deuterium oxide, δ = 2.71, J = 7, 2H), 4.53 (d, J = 4, 2H, CH_2O; becomes s with deuterium oxide), 7.43 (s, 5H, C_6H_5), 7.55 (s, 1H, H-3)
IIe	3605, 3330, 1598, 1565, 1500, 1455, 1392	0.81 (t, J = 7, 3H, CH_3), 1.1-1.8 (m, 2H, CH_2Me), 2.38 (br s, 1H, OH; disappears with deuterium oxide), 2.69 (t, J = 8, 2H, CH_2), 4.55 (s, 2H, CH_2O), 7.44 (s, 5H, C_6H_5), 7.59 (s, 1H, H-3)
IIf	3605, 3350, 1598, 1556, 1498, 1477, 1450, 1393	1.27 [d, J = 6, 6H, $(CH_3)_2C$], 2.32 (t, J = 5, 1H, OH; disappears with deuterium oxide), 3.10 (h, J = 7, 1H, $CHMe_2$), 4.66 (d, J = 5, 2H, CH_2; becomes s with deuterium oxide), 7.44 (s, 5H, C_6H_5), 7.58 (s, 1H, H-3)
IIg	3605, 3330, 1600, 1533, 1498, 1455, 1380, 1366	1.22 [s, 9H, $(CH_3)_3C$], 2.56 (t, J = 5, 1H, OH; disappears with deuterium oxide), 4.63 (d, J = 5, 2H, CH_2; becomes s with deuterium oxide), 7.40 (s, 5H, C_6H_5), 7.48 (s, 1H, H-3)
IIh	3595, 3335, 1598, 1565, 1495, 1450, 1393	2.45 (br s, 1H, OH; disappears with deuterium oxide), 4.05 (s, 2H, CH_2Ph), 4.46 (br s, 2H, CH_2O; becomes s with deuterium oxide), 6.8-7.5 (m, 10H, 2 C_6H_5), 7.65 (s, 1H, H-3)
IIi	3605, 3365, 1598, 1555, 1495, 1447, 1383	2.17 (t, J = 5.5, 1H, OH; disappears with deuterium oxide), 4.53 (d, J = 5.5, 2H, CH_2; becomes s with deuterium oxide), 7.26 and 7.31 (2 s, 10H, 2 C_6H_5), 7.80 (s, 1H, H-3)
III	3605, 3370, 1605, 1508, 1457, 1444, 1418, 1384	2.29 (t, J = 5.5, 1H, OH; disappears with deuterium oxide), 4.53 (d, J = 5.5, 2H, CH_2; becomes s with deuterium oxide), 6.7-7.5 (m, 9H, C_6H_5 + C_6H_4), 7.80 (s, 1H, H-3)

Lithium aluminum hydride reduction in diethyl ether at reflux of the easily available ethyl or methyl 1-aryl-1*H*-pyrazole-4-carboxylates **Ia-l** (in Table I only the new esters **Ib,l** are reported, along with **Ia**) gave, generally in excellent yields, 5-substituted or unsubstituted 1-aryl-1*H*-pyrazole-4-methanols **IIa-l** (Table II), whose structure was confirmed by ir and ^1H nmr spectral data (Table III).

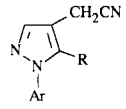
By refluxing a solution of alcohols **IIa-l** in a hydrobromic-acetic acid mixture, the corresponding 1-aryl-4-(bromomethyl)-1*H*-pyrazoles were obtained as lachrymatory, unstable liquids, which were quickly reacted with potassium cyanide in dimethyl sulfoxide solution in order to obtain the required 1-aryl-1*H*-pyrazole-4-acetonitriles **III**.

The results of this reaction were surprising, since only in the case of 5-unsubstituted compounds **IIa,b** the corresponding 1-aryl-1*H*-pyrazole-4-acetonitriles **IIIa,b** were obtained, albeit in moderate yields. In the case of **IIc-f,h-l**, mixtures of the corresponding 5-substituted 1-aryl-1*H*-pyrazole-4-acetonitriles **IIIc-f,h-l** and the isomeric 5-substituted 4-methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles **IVc-f,h-l** were found, whereas 5-*tert*-butyl derivative **IIg** gave only 3-carbonitrile **IVg**.

The above mixtures proved to be difficult to separate; we were able to resolve by silica gel chromatography the mixtures **IIIf-IVf**, **IIIh-IVh** and **IIIi-IVi**. In the case of **IIIc,d,e,l-IVc,d,e,l** mixtures, the presence of the two

Table IV

1-Aryl-1*H*-pyrazole-4-acetonitriles **IIIa,b,f,h-l**



Formula Number	R	Ar	Yield %	Mp °C or bp °C / mm	Molecular Formula	Analyses % Calcd. / Found C	H	N
IIIa	H	C_6H_5	49	32-34 [a]	$C_{11}H_9N_3$	72.11 71.93	4.95 5.00	22.93 22.68
IIIb	H	4-FC_6H_4	51	61-62 and 64-65 [a]	$C_{11}H_8FN_3$	65.66 65.67	4.01 4.01	20.88 21.00
IIIf	$CH(CH_3)_2$	C_6H_5	19	150-155 / 0.2 [b]	$C_{14}H_{15}N_3$	74.64 74.25	6.71 6.70	18.65 18.55
IIIh	$CH_2C_6H_5$	C_6H_5	15	215-220 / 0.5 [c]	$C_{18}H_{15}N_3$	79.09 79.03	5.53 5.56	15.37 15.18
IIIi	C_6H_5	C_6H_5	36	170-175 / 0.2	$C_{17}H_{13}N_3$	78.74 78.41	5.05 5.05	16.20 16.03
IIIl	C_6H_5	4-FC_6H_4	48	95-96 [a]	$C_{17}H_{12}FN_3$	73.63 73.65	4.36 4.37	15.15 15.14

[a] From diethyl ether-petroleum ether 1:1. [b] Silica gel chromatography of **IIIf** and **IVf** mixture, eluent petroleum ether-diethyl ether 3:1, gave first **IVf**, followed by **IIIf** by elution with petroleum ether-diethyl ether 2:1. [c] Silica gel chromatography of **IIIh** and **IVh** mixture, eluent petroleum ether-diethyl ether 3:1, gave first **IVh**, followed by **IIIh**.

Table V

IR and ^{1}H NMR Spectral Data of Compounds **IIIa,b,f,h-l**

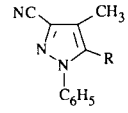
Compound	IR, cm^{-1}	^{1}H NMR, δ
IIIa	2255, 1598, 1572, 1498, 1463, 1400	3.66 (s, 2H, CH_2), 7.2-7.8 (m, 6H, C_6H_5 + H-5), 7.93 (s, 1H, H-3)
IIIb	2255, 1603, 1573, 1510, 1403	3.69 (s, 2H, CH_2), 6.95-7.85 (m, 5H, C_6H_4 + H-5), 7.91 (s, 1H, H-3)
IIIf	2255, 1600, 1564, 1502, 1478, 1458, 1402	1.30 [d, J = 7, 6H, $(CH_3)_2C$], 3.13 (h, J = 7, 1H, $CHMe_2$), 3.70 (s, 2H, CH_2), 7.49 (mc, 5H, C_6H_5), 7.64 (s, 1H, H-3)
IIIh	2250, 1600, 1566, 1495, 1452, 1402	3.36 (s, 2H, CH_2CN), 4.10 (s, 2H, CH_2Ph), 6.8-7.6 (m, 10H, 2 C_6H_5), 7.72 (s, 1H, H-3)
IIIi	2250, 1597, 1493, 1445, 1385	3.54 (s, 2H, CH_2), 7.1–7.6 (m, 10H, 2 C_6H_5), 7.83 (s, 1H, H-3)
IIIl	2250, 1606, 1510, 1460, 1445, 1415 1390	3.55 (s, 2H, CH_2), 6.8-7.6 (m, 9H, C_6H_5 + C_6H_4), 7.82 (s, 1H, H-3)

isomers was inferred from ^{1}H nmr spectra, but it was possible to isolate only compounds **IVc,d,e** and **IIIl**, namely the main component.

The structure of acetonitriles **IIIa,b,f,h-l** (Table IV) and nitriles **IVc-i** (Table VI) was proved by their ir and ^{1}H nmr spectral data (Tables V and VII, respectively). Moreover, the structure of 4,5-dimethyl-1-phenyl-1*H*-pyrazole-3-carbonitrile **IVc** was determined by its conversion to the relative carboxylic acid **VI**, followed by decarboxylation to 4,5-dimethyl-1-phenyl-1*H*-pyrazole **VII** already described [6]. Pyrazole **VII** was unequivocally synthesized by reaction of 4-hydroxy-3-methyl-3-buten-2-one [7] with phenylhydrazine, along with its isomer 3,4-dimethyl-1-phenyl-1*H*-pyrazole **VIII**, from which it could be separated by silica gel chromatography.

Table VI

5-Substituted 4-Methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles **IVc-i**



Formula Number	R	Yield %	Mp °C or bp °C / mm	Molecular Formula	Analyses % Calcd. / Found C	H	N
IVc	CH_3	29	115-117 [a]	$C_{12}H_{11}N_3$	73.07 73.34	5.62 5.69	21.30 21.01
IVd	CH_2CH_3	34	90-91 [b]	$C_{13}H_{13}N_3$	73.91 74.00	6.20 6.21	19.89 20.00
IVe	$(CH_2)_2CH_3$	35	150-155 / 0.4	$C_{14}H_{15}N_3$	74.64 74.47	6.71 6.73	18.65 18.76
IVf	$CH(CH_3)_2$	19	100-101 [b] [c]	$C_{14}H_{15}N_3$	74.64 74.73	6.71 6.68	18.65 18.74
IVg	$C(CH_3)_3$	21	123-124 [b]	$C_{15}H_{17}N_3$	75.28 75.06	7.16 7.20	17.56 17.71
IVh	$CH_2C_6H_5$	15	77-78 [d] [e]	$C_{18}H_{15}N_3$	79.09 78.94	5.53 5.55	15.37 15.11
IVi	C_6H_5	14	140-142 [d]	$C_{17}H_{13}N_3$	78.74 78.78	5.05 5.00	16.20 16.17

[a] From diethyl ether. [b] From petroleum ether-diethyl ether 1:1. [c] See footnote [b] to Table IV. [d] From 95% ethanol. [e] See footnote [c] to Table IV.

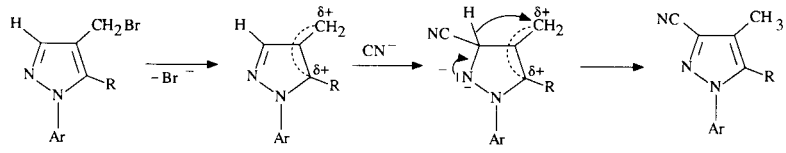
Table VII

IR and ^{1}H NMR Spectral Data of Compounds **IVc-i**

Compound	IR, cm^{-1}	^{1}H NMR, δ
IVc	2240, 1600, 1572, 1498, 1453, 1420, 1385, 1365	2.18 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 7.47 (near s, 5H, C_6H_5)
IVd	2235, 1598, 1563, 1498, 1455, 1420, 1366	1.08 (t, J = 7.5, 3H, Et CH_3), 2.22 (s, 3H, CH_3-4), 2.67 (q, J = 7.5, 2H, CH_2), 7.50 (mc, 5H, C_6H_5)
IVe	2237, 1600, 1562, 1497, 1457, 1422, 1368	0.83 (t, J = 7, 3H, Pr CH_3), 1.41 (h, J = 7, 2H, CH_2), 2.21 (s, 3H, CH_3-4), 2.65 (t, J = 7, 2H, CH_2), 7.51 (mc, 5H, C_6H_5)
IVf	2240, 1600, 1552, 1500, 1460, 1423, 1368	1.27 [d, J = 7, 6H, $(CH_3)_2C$], 2.31 (s, 3H, CH_3-4), 2.93 (h, J = 7, 1H, $CHMe_2$), 7.50 (mc, 5H, C_6H_5)
IVg	2240, 1600, 1496, 1483, 1456, 1412, 1360	1.23 [s, 9H, $(CH_3)_3C$], 2.37 (s, 3H, CH_3-4), 7.50 (mc, 5H, C_6H_5)
IVh	2237, 1598, 1562, 1492, 1450, 1427, 1365	2.15 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 6.8-7.6 (m, 10H, 2 C_6H_5)
IVi	2240, 1598, 1500, 1445, 1415, 1388, 1364	2.23 (s, 3H, CH_3), 7.30 (mc, 10H, 2 C_6H_5)

A tentative mechanism to explain the formation of nitriles **IV** (Scheme 2) involves the formation of a stabilized carbocation by ionisation of 4-bromomethyl group, followed by a nucleophilic attack of cyanide ion on C-3 of the not longer aromatic structure and migration of a hydride anion from C-3 to the carbocation to restore the aromatic system. Such a mechanism could be supported by the unsuccessful formation of nitriles **IV** when is lacking a 5-substituent, which by inductive or resonance effect can stabilize the carbocation.

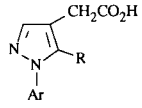
Scheme 2



Finally, acetonitriles **IIIa,b,i,l (IIIf,h** were not reacted owing to the small quantity to our disposal) were converted in 91-96% yields to the required 1-aryl-1*H*-pyrazole-4-acetic acids **Va,b,i,l** (Table VIII) by alkaline hydrolysis (potassium hydroxide in ethanol), followed by acidification.

Table VIII

1-Aryl-1*H*-pyrazole-4-acetic acids **Va,b,i,l**



Formula Number	R	Ar	Yield %	Mp °C	Molecular Formula	Analyses % Calcd. / Found C	H	N
Va	H	C_6H_5	95	108-109 [a][b]	$C_{11}H_{10}N_2O_2$	65.34 65.11	4.98 4.89	13.85 13.71
Vb	H	4-FC_6H_4	94	133-134 [c]	$C_{11}H_9FN_2O_2$	60.00 59.91	4.12 4.08	12.72 12.57
Vi	C_6H_5	C_6H_5	91	78-85 [a] [d]	$C_{17}H_{14}N_2O_2$ · 1/2 H_2O	71.07 71.21	5.26 5.23	9.75 9.77
Vl	C_6H_5	4-FC_6H_4	96	124-125 [a]	$C_{17}H_{13}FN_2O_2$	68.91 68.98	4.42 4.44	9.45 9.42

IR and ^1H NMR Spectral Data

	IR, cm^{-1}	^1H NMR, δ
Va	3100-2500, 1710, 1600, 1498, 1403	3.62 (s, 2H, CH_2), 7.2-7.8 (m, 6H, C_6H_5 + H-5), 7.92 (s, 1H, H-3), 11.06 (br s, 1H, CO_2H; disappears with deuterium oxide)
Vb	3000-2400, 1708, 1608, 1578, 1513, 1426, 1402 [e]	3.63 (s, 2H, CH_2), 6.9-7.8 (m, 5H, C_6H_4 + H-5), 7.88 (s, 1H, H-3), 11.00 (br s, 1H, CO_2H; disappears with deuterium oxide)
Vi	3000-2500, 1710, 1598, 1493, 1445, 1408, 1384	3.51 (s, 2H, CH_2), 7.27 (mc, 10H, 2 C_6H_5), 7.83 (s, 1H, H-3), 8.05 (br s, 1H, CO_2H; disappears with deuterium oxide)
Vl	3000-2500, 1712, 1607, 1510, 1458, 1445, 1413, 1388	3.52 (s, 2H, CH_2), 6.7-7.7 (m, 9H, C_6H_5 + C_6H_4), 7.85 (s, 1H, H-3), 9.51 (br s, 1H, CO_2H; disappears with deuterium oxide)

[a] From diethyl ether-petroleum ether 1:1. [b] Reference [3], mp 109 °C. [c] From diethyl ether. [d] Reference [4], mp 107-110 °C. [e] In potassium bromide.

Acids **Va,b,i,l** were screened *in vivo* for their analgesic and antiinflammatory activities, as well as for their behavioral effects and acute toxicity by known methods [8] (Table IX). Compounds **Vb, Vi** and **Vl** produced a statistically significant antinociceptive effect in the acetic acid writhing test. The degree of protection was 90-96% and was of the same order as that afforded by the equitoxic dose of dipyrone; only compound **Va** was inactive. However, when the hot plate test was used to verify the analgesic activity of the above compounds, none of them exerted a statistically significant effect.

Table IX

Pharmacological data of compounds **Va, Vb, Vi** and **Vl**

Comp.	Approximate oral LD_{50} in mice (mg/kg)	Analgesic activity in mice		Antiinflammatory activity in rats [b]	
		Writhing test [a]	Hot plate test [a]	Edema μl mean ± SD	Inhibition %
Va	999	70	6	176 ± 21	-16
Vb	1900	90 [c] [*]	13	129 ± 26	14
Vi	999	90 [c] [*]	6	119 ± 52	21
Vl	1400	96 [c] [#]	6	99 ± 30 [c] [+]	34
aspirin	800	67	33	[d]	[d]
dipyrone	3120	92 [c] [*]	80 [c] [§]	[d]	[d]
indomethacin	25	[d]	[d]	13 ± 52 [†]	91

[a] Per cent protection produced by oral administration of 1/4 LD_{50}. [b] Carrageenan paw edema test (control value 151 ± 30 μl); effect produced by oral administration of 1/4 LD_{50}. [c] Statistical significance *versus* controls was evaluated by the Wilcoxon two sample test for writhing test, by the Fisher exact test for hot plate test and by the Student test for antiinflammatory activity; [§] $p<0.05$, [*] $p<0.02$, [+] $p<0.01$, [#] $p<0.002$, [†] $p<0.001$. [d] Not determinated.

Only compound **Vl** exhibited a statistically significant antiinflammatory effect in the carrageenan-induced edema assay, affording a 34% protection; with equitoxic dose of indomethacin, the protection was 91%.

Concerning the behavioral effects, evaluated in mice with the Morpurgo modification [9] of Irwin multidimensional screening procedure, the highest tested doses of **Va, Vb** and **Vi** produced marked depression of central nervous system, death generally occurring by respiratory failure between 2 and 7 days after treatment; with subtoxic doses, no signs of depression were observed. In contrast, with high doses of **Vl**, generalized tremors stimulated by noise and manipulation and tonic-clonic self-limited convulsions were observed, along with depression sign (hypoactivity, passivity and ptosis); at lower subtoxic dosages, no evident effects on central nervous system were noted.

EXPERIMENTAL

The ir spectra were measured in chloroform solution with a Perkin-Elmer Model 398 spectrophotometer and the ^1H nmr spectra were recorded in deuteriochloroform solution on a Hitachi Perkin-Elmer Model R-600 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a

Fisher-Johns apparatus.

General Procedure for Ethyl 1-Aryl-1*H*-pyrazole-4-carboxylates **Ia,b**.

To ethyl 2,2-diformylacetate [10] (7.2 g, 50 mmoles) dissolved in anhydrous ethanol (150 ml) was added a solution of phenylhydrazine or 4-fluorophenylhydrazine (53 mmoles) in anhydrous ethanol (50 ml) containing acetic acid (5 ml). The solution was refluxed for 2 hours, evaporated under reduced pressure and the residue was extracted with chloroform. The extracts were washed once with saturated sodium hydrogen carbonate solution and water, dried (magnesium sulfate) and evaporated under reduced pressure to give a solid residue which was recrystallized from 95% ethanol.

Elemental analyses, yields, mps, ir and ^{1}H nmr spectral data of esters **Ia,b** are reported in Table I.

Ethyl 1-(4-Fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate (**Il**).

This compound (Table I) was prepared from ethyl 2-(dimethylamino)methylene-3-oxo-3-phenyl propanoate and 4-fluorophenylhydrazine following a general procedure already described [1].

General Procedure for 5-Substituted or Unsubstituted 1-Aryl-1*H*-pyrazole-4-methanols **IIa-l**.

Ethyl or methyl 1-aryl-1*H*-pyrazole-4-carboxylates **Ia-l** (for esters **Ic-i**, see reference [1]) (20 mmoles) dissolved in anhydrous diethyl ether (200-300 ml) were slowly added to a stirred solution of lithium aluminum hydride (1.52 g, 40 mmoles) in the same solvent (150 ml). The mixture was refluxed for 7 hours, stirred overnight at room temperature, cooled with ice and treated in succession with water (2 ml), 10% sodium hydroxide solution (4 ml) and water (10 ml). The resulting mixture was filtered, the inorganic precipitate was washed three times with diethyl ether, the solution plus washings were dried (magnesium sulfate) and evaporated under reduced pressure to give a residue which was purified by recrystallization from a suitable solvent or by bulb-to-bulb distillation *in vacuo*.

Elemental analyses, yields, mps or bps of these compounds are reported in Table II; ir and ^{1}H nmr spectral data in Table III.

General Procedure for 5-Substituted or Unsubstituted 1-Aryl-1*H*-pyrazole-4-acetonitriles **IIIa,b,f,h-l** and 5-Substituted 4-Methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles **IVc-i**.

Pyrazoles **IIa-l** (10 mmoles) were added to acetic acid (100 ml) containing 48% hydrobromic acid (20 ml), the resulting solution was refluxed for 15 hours and evaporated under reduced pressure. The residue was extracted with chloroform (100 ml), the solution was washed with 10% sodium carbonate and with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residues were lachrimatory, unstable liquids which decomposed on attempted distillation *in vacuo* and also by standing; therefore they were quickly dissolved in anhydrous dimethyl sulfoxide (50 ml). The solution was slowly added to a stirred solution of potassium cyanide (0.72 g, 11 mmoles) in the same solvent (20 ml) heated at ~90°, the heating bath being removed just before the addition. The mixture was stirred at room temperature for 10 minutes, cooled at 0°, diluted with water (70 ml) and extracted three times with chloroform (50 ml each time). The extracts were washed with 6*N* hydrochloric acid and water, dried (magnesium sulfate) and evaporated under reduced pressure. A preliminary purification of the residues was achieved by chromatography on florisil, using diethyl ether as eluent.

The ^{1}H nmr spectra of these residues revealed that in most cases they were mixtures of nitriles **III** and **IV** in variable amounts, only **IIIa**, **IIIb** and **IVg** being single isomers. Silica gel chromatography, eluent petroleum ether (bp 40-70°)-diethyl ether 3:1, separated isomers **III** and **IV** only when both compounds were in an approximately 1:1 or 2:1 mixture, **III**, **IVf,h,i**; in the other cases, only the most abundant isomer was isolated, **IIIl**; **IVc,d,e**. In particular, **IVi** (about 2:1 **IIIi**:**IVi** mixture) was obtained by diluting the purified liquid residue with a little 95% ethanol, cooling the solution and filtering the precipitate; **IIIi** was recovered from the liquid filtrate by silica gel chromatography.

Elemental analyses, yields, mps or bps of nitriles **IIIa,b,f,h,i,l** are reported in Table IV; ir and ^{1}H nmr spectral data in Table V.

Elemental analyses, yields, mps or bps of nitriles **IVc-i** are reported in Table VI; ir and ^{1}H nmr spectral data in Table VII.

General Procedure for 1-Aryl-1*H*-pyrazole-4-acetic Acids **Va,b,i,l**.

A solution of nitriles **IIIa,b,i,l** (10 mmoles) in 95% ethanol (10 ml) and 20% potassium hydroxide (30 ml) was refluxed for 10 hours. After cooling, the solution was diluted with water (30 ml), extracted with diethyl ether, acidified with 6*N* hydrochloric acid (*p*H ~1) and the precipitate was extracted thoroughly with chloroform. The extracts were washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to give a solid residue which was recrystallized from a suitable solvent.

Elemental analyses, yields, mps, recrystallization solvents, ir and ^{1}H nmr spectral data of these acids are reported in Table VIII.

4,5-Dimethyl-1-phenyl-1*H*-pyrazole-3-carboxylic Acid (**VI**).

This acid was obtained in 95% yield starting from **IVc** and following the above general procedure; white needles, mp 164-165° from diethyl ether; ir (chloroform): ν max 3000-2500, 1753, 1692, 1600, 1565, 1500, 1460, 1438, 1385, 1370 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 7.52 (s, 5H, C_6H_5), 11.45 (br s, 1H, CO_2H; disappears with deuterium oxide).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.88; H, 5.59; N, 12.98.

4,5-Dimethyl-1-phenyl-1*H*-pyrazole (**VII**).

Acid **VI** (0.65 g, 3 mmoles) was decarboxylated by heating at 180° for 10 hours, distilling *in vacuo* the decarboxylated product after 5 and 10 hours; colorless liquid, bp 103-105°/0.5 (reference [6], 141°/11); yield, 0.38 g (73%); ir (chloroform): ν max 1598, 1577, 1500, 1482, 1453, 1388 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 7.47 (near s, 6H, C_6H_5 + H-3).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.36; H, 6.98; N, 16.50.

Preparation of **VII** and 3,4-Dimethyl-1-phenyl-1*H*-pyrazole (**VIII**).

Phenylhydrazine (3.46 g, 32 mmoles) dissolved in anhydrous ethanol (20 ml) was added to a solution of 4-hydroxy-3-methyl-3-buten-2-one [7] (3.0 g, 30 mmoles) in anhydrous ethanol (60 ml) containing acetic acid (2 ml). The resulting solution was refluxed for 2 hours and evaporated under reduced pressure to give a liquid residue which was dissolved in chloroform. The solution was washed with saturated sodium hydrogen carbonate solution

in water, dried (magnesium sulfate) and evaporated under reduced pressure. The liquid residue was purified by bulb-to-bulb distillation *in vacuo* to give a colorless liquid, bp 105-110°/0.6; yield, 4.72 g (85%). As resulted from its ^{1}H nmr spectrum, this liquid was a ~2:1 mixture of **VIII**:**VII**, which was separated by silica gel chromatography, eluent petroleum ether-diethyl ether 9:1.

Pyrazole **VIII** was eluted first as a colorless liquid, bp 100-105°/0.6 (reference [6], 148°/11); ir (chloroform): ν max 1597, 1574, 1498, 1482, 1460, 1407, 1377, 1360, 1332 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.06 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 7.1-7.8 (m, 6H, C_6H_5 + H-5).

Pyrazole **VII** was eluted successively and showed ir and ^{1}H nmr spectra superimposable with those of the product obtained by decarboxylation of acid **VI**.

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