ω-Dialkylaminoalkyl Ethers of Phenyl-(5-substituted 1-phenyl-1*H*-pyrazol-4-yl)methanols with Analgesic and Anti-inflammatory Activity

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A series of carbinols **3a-f** was prepared starting from methanols **1a-f** *via* oxidation with pyridinium chlorochromate to aldehydes **2a-f**, followed by a Grignard reaction of the latter. Reaction of **3a-f** with ω-chloroalkyldialkylamine hydrochlorides afforded a series of aminoether derivatives **4g-t**. Compounds **4i,m-p,s** showed a good analgesic activity in the acetic acid writhing test in mice. Moreover, compounds **4h,l,s** exhibited a moderate anti-inflammatory activity in the carrageenan-induced edema assay in rats.

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The synthesis and pharmacological evaluation of numerous molecules with 1-aryl-1*H*-pyrazole nucleus were reported in our previous works. In the majority of these compounds position 3 or 4 of the heterocyclic ring bore an acid substituent: carboxylic group or acetic or propionic moiety. Many of them proved to be interesting for their anti-inflammatory, analgesic and platelet antiaggregating activities [1-4].

In one of the above papers, we reported the synthesis of 5-substituted 1-aryl-1*H*-pyrazole-4-methanols **1a-f**, as intermediates to prepare 5-substituted 1-aryl-1*H*-pyrazole-4-acetic acids with appreciable analgesic and anti-inflammatory properties [3].

Recently, a French patent reported the analgesic activity found in aryl-(heteroaryl)carbinols and their aminoether derivatives [5]. In many of these compounds the heteroaryl moiety was represented by a 1-alkyl-1*H*-pyrazole nucleus and, in the aminoether derivatives, the side chain in position 4 or 5 of the heterocyclic ring was characterized by an aliphatic tertiary amino group, separated from the oxygen atom by a two or three carbon chain. In particular, compound E-3710 (Figure 1) emerged as a potent analgesic, which was then submitted to phase I in clinical trials as citrate salt (E-4018) [6].

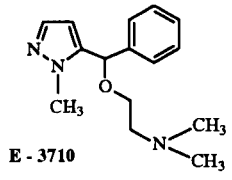
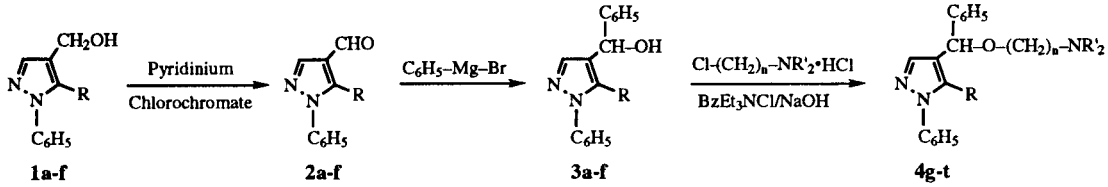


Figure 1

On this basis and so as to gain further information on the structural activity relationship of the 1-aryl-1*H*-pyrazole derivatives, we planned the synthesis of a new series of 1-phenyl-1*H*-pyrazoles **4g-t**. With this goal, we employed the above mentioned intermediates **1a-f** to introduce a basic chain in position 4 of the pyrazole nucleus, in analogy with the patent compounds.

Pyridinium chlorochromate oxidation [7] of 5-substituted 1-phenyl-1*H*-pyrazole-4-methanols **1a-f**, in anhydrous dichloromethane at room temperature, gave 5-substituted

Scheme



	R
a	CH_3
b	C_2H_5
c	$(CH_2)_2CH_3$
d	$CH(CH_3)_2$
e	$C(CH_3)_3$
f	C_6H_5

	R	n	NR'_2
g	C_6H_5	2	$N(CH_3)_2$
h	CH_3	3	$N(CH_3)_2$
i	$(CH_2)_2CH_3$	3	$N(CH_3)_2$
j	$CH(CH_3)_2$	3	$N(CH_3)_2$
k	$C(CH_3)_3$	3	$N(CH_3)_2$
l	C_6H_5	3	$N(CH_3)_2$

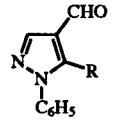
	R	n	NR'_2
o	CH_3	2	N⟨ ⟩
p	$(CH_2)_2CH_3$	2	N⟨ ⟩
q	C_6H_5	2	N⟨ ⟩
r	CH_3	3	N⟨ ⟩
s	CH_2CH_3	3	N⟨ ⟩
t	$C(CH_3)_3$	3	N⟨ ⟩

1-phenyl-1*H*-pyrazole-4-carboxaldehydes **2a-f**, in excellent yields (Table I).

By reaction of aldehydes **2** with phenylmagnesium bromide, the corresponding phenyl-(5-substituted 1-phenyl-1*H*-pyrazol-4-yl)methanols **3a-f** were generally obtained in good yields (Table II).

Table I

5-Substituted 1-Phenyl-1*H*-pyrazole-4-carboxaldehydes **2 a-f**



Compound	R	Yield %	Mp °C or bp °C (mm Hg)	Molecular Formula	Analyses % Calcd./Found C	H	N
2a	CH_3	90	74-75 [a] [b]	$C_{11}H_{10}N_2O$	70.95	5.41	15.04
					70.97	5.42	15.16
2b	C_2H_5	89	56-57 [c]	$C_{12}H_{12}N_2O$	71.98	6.04	13.99
					71.76	5.98	13.87
2c	$(CH_2)_2CH_3$	88	130-135 (0.07)	$C_{13}H_{14}N_2O$	72.87	6.58	13.07
					72.78	6.60	13.32
2d	$CH(CH_3)_2$	92	79-80 [a]	$C_{13}H_{14}N_2O$	72.87	6.58	13.07
					72.85	6.55	13.00
2e	$C(CH_3)_3$	90	86-87 [a]	$C_{14}H_{16}N_2O$	73.66	7.06	12.27
					73.40	7.00	12.13
2f	C_6H_5	95	113-114 [c] [d]	$C_{16}H_{12}N_2O$	77.40	4.87	11.28
					77.22	4.83	11.59

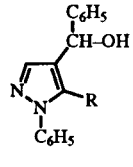
IR and ^{1}H-NMR Spectral Data

Compound	IR, cm^{-1} ($CHCl_3$)	^{1}H-NMR, δ (deuteriochloroform)
2a	2835, 2740, 1677	2.60 (*s*, 3H, CH_3), 7.54 (m, 5H, C_6H_5), 8.12 (*s*, 1H, H-3), 10.03 (*s*, 1H, CHO)
2b	2840, 2740, 1672	1.19 (t, J = 7.2, 3H, CH_3), 2.49 (q, J = 7.2, 2H, CH_2), 7.53 (m, 5H, C_6H_5), 8.11 (*s*, 1H, H-3), 10.05 (*s*, 1H, CHO)
2c	2835, 2735, 1675	0.88 (t, J = 7.5, 3H, CH_3), 1.25-2.0 (m, 2H, CH_2), 2.97 (near t, J = 7.5, 2H, CH_2), 7.53 (m, 5H, C_6H_5), 8.12 (*s*, 1H, H-3), 10.01 (*s*, 1H, CHO)
2d	2840, 2735, 1665	1.38 [d, J = 7, 6H, $(CH_3)_2C$], 3.24 (h, J = 7, 1H, $CHMe_2$), 7.54 (m, 5H, C_6H_5), 8.12 (*s*, 1H, H-3), 10.15 (*s*, 1H, CHO)
2e	2870, 2740, 1688	1.34 [s, 9H, $(CH_3)_3C$], 7.2-7.7 (m, 5H, C_6H_5), 8.14 (*s*, 1H, H-3), 10.25 (*s*, 1H, CHO)
2f	2835, 2745, 1673	7.1-7.6 (m, 10H, $2C_6H_5$), 8.30 (*s*, 1H, H-3), 9.82 (*s*, 1H, CHO)

[a] From petroleum ether (bp 40-70°C). [b] References [8] and [9], mp 68-70°C. [c] From diethyl ether/petroleum ether (bp 40-70°C). [d] Reference [9], mp 90-93°C.

Table II

Phenyl-(5-substituted 1-phenyl-1H-pyrazol-4-yl)methanols **3 a-f**



Compound	R	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
3a	CH_3	78	125-126 [a]	$C_{17}H_{16}N_2O$	77.25	6.10	10.60
					77.09	6.13	10.52
3b	C_2H_5	62	138-139 [b]	$C_{18}H_{18}N_2O$	77.67	6.51	10.06
					77.43	6.51	10.05
3c	$(CH_2)_2CH_3$	71	117-118 [b]	$C_{19}H_{20}N_2O$	78.05	6.89	9.58
					77.83	6.82	9.49

Table II (continued)

Compound	R	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
3d	$CH(CH_3)_2$	75	159-160 [c]	$C_{19}H_{20}N_2O$	78.05	6.89	9.58
					77.81	6.87	9.45
3e	$C(CH_3)_3$	79	153-154 [b]	$C_{20}H_{22}N_2O$	78.40	7.24	9.14
					78.49	7.33	9.07
3f	C_6H_5	82	188-189 [c]	$C_{22}H_{18}N_2O$	80.96	5.56	8.58
					80.84	5.61	8.63

IR and ^{1}H-NMR Spectral Data

Compound	IR, cm^{-1} (potassium bromide)	^{1}H-NMR, δ (deuteriochloroform)
3a	3250	2.25 (s, 3H, CH_3), 2.85 (d, J = 4.8, 1H, OH; disappears with deuterium oxide), 5.84 (d, J = 4.8, 1H, CH-O; becomes *s* with deuterium oxide), 7.45 (m, 11H, $2C_6H_5$ + H-3)
3b	3225	0.97 (t, J = 7, 3H, CH_3), 2.68 (q, J = 7, 2H, CH_2), 2.91 (d, J = 4, 1H, OH; disappears with deuterium oxide), 5.85 (d, J = 4, 1H, CH-O; becomes *s* with deuterium oxide), 7.48 (m, 11H, $2C_6H_5$ + H-3)
3c	3235	0.77 (t, J = 7, 3H, CH_3), 1.05-1.65 (m, 2H, CH_2Me), 2.45-2.9 (m, 3H, CH_2 + OH; 1H disappears with deuterium oxide, m becomes t, J = 7), 5.88 (d, J = 3.5, 1H, CH-O; becomes *s* with deuterium oxide), 7.48 (m, 11H, $2C_6H_5$ + H-3)
3d	3255	1.22 and 1.34 [2d, J = 7.2, 6H, $(CH_3)_2C$], 2.57 (d, J = 4.2, 1H, OH; disappears with deuterium oxide), 3.18 (h, J = 7.2, 1H, $CHMe_2$), 6.09 (d, J = 4.2, 1H, CH-O; becomes *s* with deuterium oxide), 7.38 (s, 1H, H-3), 7.48 (m, 10H, $2C_6H_5$)
3e	3350	1.27 [s, 9H, $(CH_3)_3C$], 2.41 (d, J = 4.8, 1H, OH; disappears with deuterium oxide), 6.74 (d, J = 4.8, 1H, CH-O; becomes *s* with deuterium oxide), 7.33 (s, 1H, H-3), 7.46 (m, 10H, $2C_6H_5$)
3f	3265	2.55 (d, J = 4, 1H, OH; disappears with deuterium oxide), 5.73 (d, J = 4, 1H, CH-O; becomes *s* with deuterium oxide), 7.1-7.5 (m, 15H, $3C_6H_5$), 7.65 (s, 1H, H-3)

[a] From diethyl ether. [b] From diethyl ether/petroleum ether (bp 40-70°C). [c] From ethyl acetate.

Finally, carbinols **3** were converted to their ω-dialkylaminoalkyl ethers **4g-t** by a phase transfer reaction with the appropriate ω-chloroalkyldialkylamine hydrochloride in the presence of benzyltriethylammonium chloride as catalyst, in a two-phase system (toluene/50% sodium hydroxide) (Tables III and IV).

All attempts to convert the aminoethers **4** to their hydrochlorides, in order to obtain water soluble derivatives, caused the cleavage of the ether bond; therefore these compounds were pharmacologically tested as free bases in a 0.5% carboxymethylcellulose suspension.

Compounds **3** and **4g-q,s,t** were screened *in vivo* for their anti-inflammatory and analgesic activities. The results of the pharmacological evaluation of the more interesting derivatives are listed in Table V.

All carbinols **3** resulted completly inactive.

Among aminoethers, compounds **4h,l,s** showed a statistically significant anti-inflammatory activity in the carrageenan-induced edema assay, using indomethacin as a reference standard. The degree of protection was 30% for **4h**, 40% for **4l** and 26% for **4s** at the dose of 200 mg/kg; none of them showed a significant anti-inflammatory effect at the dose of 100 mg/kg.

Compounds **4i,m-p,s** exhibited a good antinociceptive activity in the writhing test. The degree of protection ranged from 29% to 61% at the dose of 200 mg/kg, using dipyrone as a reference standard. The most active aminoethers **4m-p** were further tested at doses decreasing by factor 2 and afforded a statistically significant effect also at 100 mg/kg.

In conclusion, the analgesic effect previously observed in a number of 1-phenyl-1*H*-pyrazole derivatives [1-4] was confirmed in this new series **4**, in which position 4 of the heterocyclic nucleus is substituted with an aminoether chain. This result is in agreement with the data reported in the above mentioned patent [6].

The lack of anti-inflammatory activity in these derivatives seems to be further proof that an acid function is necessary on the pyrazole nucleus, so that the anti-inflammatory activity can be present.

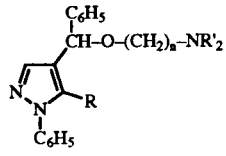
EXPERIMENTAL

a) Chemistry.

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. The ir spectra were registered on a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded on a Hitachi Perkin-Elmer R-600 instrument (60 MHz); chemical shifts are reported as δ (ppm) relative to TMS as an internal standard; J in Hz. The elemental analyses were

Table III

ω-Dialkylaminoalkyl Ethers of Phenyl-(5-substituted 1-phenyl-1*H*-pyrazol-4-yl)methanols **4g-t**



Compound	R	n	NR'_2	Reaction time (days)	Yield %	Bp °C (mm Hg) or mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
4g	C_6H_5	2	$N(CH_3)_2$	7[a]	52	190-195 (0.08)	$C_{26}H_{27}N_3O$	78.56	6.85	10.57
								78.46	7.00	10.80
4h	CH_3	3	$N(CH_3)_2$	2[b]+3[c]	43	213-215 (0.3)	$C_{22}H_{27}N_3O$	75.61	7.79	12.02
								75.32	7.75	12.26
4i	$(CH_2)_2CH_3$	3	$N(CH_3)_2$	2[b]+4[c]	43	185-190 (0.15)	$C_{24}H_{31}N_3O$	76.35	8.28	11.13
								76.07	8.32	11.40
4l	$CH(CH_3)_2$	3	$N(CH_3)_2$	2[b]+5[c]	42	178-180 (0.2)	$C_{24}H_{31}N_3O$	76.35	8.28	11.13
								76.28	8.29	11.34
4m	$C(CH_3)_3$	3	$N(CH_3)_2$	5[b]+2[c]	25	93-94 [d]	$C_{25}H_{33}N_3O$	76.69	8.49	10.73
								76.62	8.54	10.70
4n	C_6H_5	3	$N(CH_3)_2$	2[b]+3[c]	70	190-192 (0.2)	$C_{27}H_{29}N_3O$	78.80	7.10	10.21
								78.91	7.10	10.51
4o	CH_3	2	N◯	3[a]+3[c]	81	205-210 (0.3)	$C_{24}H_{29}N_3O$	76.76	7.78	11.19
								76.47	7.76	11.49
4p	$(CH_2)_2CH_3$	2	N◯	3[a]+3[c]	67	190-193 (0.08)	$C_{26}H_{33}N_3O$	77.38	8.24	10.41
								77.36	8.30	10.65
4q	C_6H_5	2	N◯	3[a]+2[c]	82	230-235 (0.2)	$C_{29}H_{31}N_3O$	79.60	7.14	9.60
								79.48	7.40	9.90
4r	CH_3	3	N◯	3[a]+2[c]	66	210-215 (0.4)	$C_{25}H_{31}N_3O$	77.08	8.02	10.79
								77.08	8.05	11.06
4s	C2H5	3	N◯	4[b]+2[c]	57	218-223 (0.3) 68-70 [e]	$C_{26}H_{33}N_3O$	77.38	8.24	10.41
								77.16	8.19	10.68
4t	$C(CH_3)_3$	3	N◯	3[b]+2[c]	76	102-103 [e]	$C_{28}H_{37}N_3O$	77.92	8.64	9.73
								78.02	8.74	9.60

[a] At room temperature. [b] At 80°C. [c] At 140°C. [d] From diethyl ether/petroleum ether (bp 40-70°C). [e] From petroleum ether (bp 40-70°C).

Table IV

IR and ^{1}H-NMR Spectral Data of Compounds **4g-t**

Compound	IR, cm^{-1} ($CHCl_3$)	^{1}H-NMR, δ ($CDCl_3$)
4g	2865, 2825, 2780	2.21 [s, 6H, $(CH_3)_2N$], 2.50 (t, J = 6.5, 2H, CH_2N), 3.47 (t, J = 6.5, 2H, CH_2O), 5.27 (s, 1H, CHO), 7.26 (s, 5H, C_6H_5-5), 7.39 (m, 10H, $2C_6H_5$), 7.63 (s, 1H, H-3)
4h	2855, 2820, 2770	1.6-2.0 (m, 2H, CH_2), 2.23 [s, 6H, $(CH_3)_2N$], 2.30 (s, 3H, CH_3), 2.3-2.6 (m, 2H, CH_2N), 3.55 (t, J = 6.5, 2H, CH_2O), 5.42 (s, 1H, CHO), 7.48 (m, 11H, $2C_6H_5$ + H-3)
4i	2860, 2820, 2775	0.78 (t, J = 7, 3H, CH_3), 1.05-2.1 (m, 4H, $2CH_2$), 2.20 [s, 6H, $(CH_3)_2N$], 2.2-2.9 (m, 4H, $CH_2N + CH_2$), 3.52 (t, J = 6.5, 2H, CH_2O), 5.41 (s, 1H, CHO), 7.45 (m, 11H, $2C_6H_5$ + H-3)
4l	2865, 2825, 2775	1.19 and 1.31 [2d, J = 5.5, 6H, $(CH_3)_2C$], 1.6-2.0 (m, 2H, CH_2), 2.05-2.6 (m, 2H, CH_2N), 2.22 [s, 6H, $(CH_3)_2N$], 2.8-3.4 (m, 1H, $CHMe_2$), 3.55 (t, J = 6.5, 2H, CH_2O), 5.59 (s, 1H, CHO), 7.37 (s, 1H, H-3), 7.47 (m, 10H, $2C_6H_5$)
4m	2860, 2820, 2775	1.23 [s, 9H, $(CH_3)_3C$], 1.65-2.0 (m, 2H, CH_2), 2.20 [s, 6H, $(CH_3)_2N$], 2.2-2.6 (m, 2H, CH_2N), 3.55 (t, J = 6.5, 2H, CH_2O), 5.70 (s, 1H, CHO), 7.23 (s, 1H, H-3), 7.41 (m, 10H, 2 C_6H_5)
4n	2865, 2825, 2780	1.4-2.0 (m, 2H, CH_2), 2.20 [s, 6H, $(CH_3)_2N$], 2.2-2.6 (m, 2H, CH_2N), 3.43 (t, J = 6.5, 2H, CH_2O), 5.26 (s, 1H, CHO), 7.28 (s, 5H, C_6H_5-5), 7.39 (m, 10H, $2C_6H_5$), 7.63 (s, 1H, H-3)
4o	2855, 2825, 2790	1.3-1.85 (m, 6H, $3CH_2$ pip), 2.31 (s, 3H, CH_3), 2.46 (m, 4H, $2CH_2N$ pip), 2.63 (t, J = 6.5, 2H, CH_2N), 3.62 (t, J = 6.5, 2H, CH_2O), 5.47 (s, 1H, CHO), 7.46 (m, 11H, $2C_6H_5$ + H-3)
4p	2855, 2825, 2790	0.78 (t, J = 7, 3H, CH_3), 1.05-1.8 (m, 8H, $3CH_2$ pip + CH_2Me), 2.3-2.85 (m, 8H, $3CH_2N + CH_2$), 3.64 (t, J = 6.5, 2H, CH_2O), 5.48 (s, 1H, CHO), 7.45 (m, 11H, $2C_6H_5$ + H-3)

Table IV (continued)

Compound	IR, cm $^{-1}$ ($CHCl_3$)	^{1}H-NMR, δ ($CDCl_3$)
4q	2865, 2825, 2795	1.3-1.8 (m, 6H, $3CH_2$ pip), 2.38 (m, 4H, $2CH_2N$ pip), 2.55 (t, J = 6.5, 2H, CH_2N), 3.52 (t, J = 6.5, 2H, CH_2O), 5.32 (s, 1H, CHO), 7.26 (s, 5H, C_6H_5-5), 7.36 (m, 10H, $2C_6H_5$), 7.64 (s, 1H, H-3)
4r	2855, 2810, 2775	1.3-2.0 (m, 8H, $3CH_2$ pip + CH_2), 2.29 (s, 3H, CH_3), 2.3-2.6 (m, 6H, $3CH_2N$), 3.52 (t, J = 6.5, 2H, CH_2O), 5.40 (s, 1H, CHO), 7.47 (m, 11H, $2C_6H_5$ + H-3)
4s	2850, 2805, 2770	1.00 (t, J = 7, 3H, CH_3), 1.3-2.1 (m, 8H, $3CH_2$ pip + CH_2), 2.2-2.6 (m, 6H, $3CH_2N$), 2.71 (q, J = 7, 2H, CH_2Me), 3.52 (t, J = 6.5, 2H, CH_2O), 5.42 (s, 1H, CHO), 7.45 (m, 11H, $2C_6H_5$ + H-3)
4t	2855, 2810, 2770	1.25 [s, 9H, $(CH_3)_3C$], 1.4-2.1 (m, 8H, $3CH_2$ pip + CH_2), 2.2-2.65 (m, 6H, $3CH_2N$), 3.52 (t, J = 6.5, 2H, CH_2O), 5.70 (s, 1H, CHO), 7.21 (s, 1H, H-3), 7.43 (m, 10H, $2C_6H_5$)

Table V

Pharmacological data of compounds **4h-p, s**

Compound	Tested dose (mg/kg p. o.)	Analgesic activity in mice	Anti-inflammatory activity in rats [b]	
		Writhing test [a]	Edema (μl) (mean ± S.D.)	Inhibition (%)
4h	200	-	221 ± 26 * [c]	30
	100	n. d. [d]	277 ± 36	15
4i	200	41 * [c]	321 ± 22	-
	100	18	n. d. [d]	n. d. [d]
4l	200	19	189 ± 22 * [c]	40
	100	n. d. [d]	269 ± 56	12
4m	200	61 * [c]	296 ± 18	-
	100	40 * [c]	n. d. [d]	n. d. [d]
	50	18	n. d. [d]	n. d. [d]
4n	200	51 * [c]	284 ± 35	10
	100	22 ** [c]	n. d. [d]	n. d. [d]
	50	8	n. d. [d]	n. d. [d]
4o	200	54 * [c]	289 ± 31	8
	100	24 ** [c]	n. d. [d]	n. d. [d]
	50	10	n. d. [d]	n. d. [d]
4p	200	55 * [c]	306 ± 58	3
	100	38 * [c]	n. d. [d]	n. d. [d]
	50	15	n. d. [d]	n. d. [d]
4s	200	29 * [c]	233 ± 51 * [c]	26
	100	11	290 ± 33	8
dipyrone	200	70 * [c]	n. d. [d]	n. d. [d]
	100	58 * [c]	n. d. [d]	n. d. [d]
indomethacin	10	n. d. [d]	79 ± 32 * [c]	75
	5	n. d. [d]	142 ± 41 * [c]	55

[a] Per cent protection. [b] Carrageenan paw edema test (control value 315 ± 34). [c] Statistical significance *versus* control group was evaluated by the Student's test: * $p < 0.01$; ** $p < 0.05$. [d] n. d., not determinated.

performed at the Microanalytical Laboratory of the "Istituto di Scienze Farmaceutiche" of Genova University using a Carlo Erba Elemental Analyzer Model 1106.

General Procedure for 5-Substituted 1-Phenyl-1*H*-pyrazole-4-carboxaldehydes **2a-f.**

Alcohols **1a-f** (20 mmoles) dissolved in anhydrous dichloromethane (10 ml) were added to a magnetically stirred suspension of pyridinium chlorochromate (6.46 g, 30 mmoles) in the same solvent (50 ml). The resulting mixture was stirred at room temperature for 1.5 hours and, therefore, diluted with anhydrous diethyl ether (50 ml). The supernatant organic solution was decanted from a black gum and the insoluble residue was washed with anhydrous diethyl ether (3 x 10 ml). The combined organic solution was filtered on florisil and the solvent was removed by distillation. The crude residues were purified by recrystallization from a suitable solvent for compounds **2a,b,d-f** or by bulb-to-bulb distillation *in vacuo* for compound **2c**.

Yields, melting points or boiling points, recrystallization solvents, ir and ^{1}H nmr spectral data of aldehydes **2a-f** are reported in Table I.

General Procedure for Phenyl-(5-substituted 1-phenyl-1*H*-pyrazol-4-yl)methanols **3a-f.**

Aldehydes **2a-f** (20 mmoles) dissolved in anhydrous diethyl ether, for compounds **3a,c,e,f** or tetrahydrofuran, for compounds **3b,d**, (80 ml) were slowly added with stirring to an ice-cooled solution of phenylmagnesium bromide, prepared from magnesium turnings (1.46 g, 60 mmoles) and bromobenzene (7.22 g, 46 mmoles) in the same solvent (100 ml). The mixture was refluxed for 24 hours, cooled at 0°C, diluted with chloroform (100 ml) and treated with 15% sulfuric acid (*p*H~1). The organic layer was separated from the

acid phase, which was extracted thoroughly with chloroform. The combined organic solution was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to give a white solid residue, which was purified by recrystallization from a suitable solvent.

Yields, melting points, recrystallization solvents, ir and ^{1}H nmr spectral data of alcohols **3a-f** are reported in Table II.

General Procedure for ω-Dialkylaminoalkyl Ethers of Phenyl-(5-substituted 1-Phenyl-1*H*-pyrazol-4-yl)methanols **4g-t.**

A solution of alcohols **3a-f** (10 mmoles) in toluene (40 ml) was added to a 50% sodium hydroxide solution (20 ml) containing the appropriate ω-chloroalkyldialkylamine hydrochloride (140 mmoles) and benzyltriethylammonium chloride (50 mg). After stirring for a certain time at a suitable temperature (Table III), the mixture was cooled and the basic layer diluted with water (20 ml), separated from the organic solution and extracted thoroughly with chloroform. The combined organic solution was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to give a residue, which was purified by sylica gel chromatography, using in succession petroleum ether (bp 40-70°C)-ethyl acetate 1:1 and ethyl acetate as eluants.

The residue obtained from ethyl acetate eluates was further purified by bulb-to-bulb distillation *in vacuo* for compounds **4g-l,n-r** or by recrystallization from petroleum ether (bp 40-70°C) for compounds **4m,s,t.**

Yields, boiling points or melting points, ir and ^{1}H nmr spectral data of aminoethers **4g-t** are reported in Table III.

b) Pharmacology.

Swiss male albino mice (22-30 g) and Sprague-Dawley male rats (100-120 g) were used. The animals were not fed for about 12 hours before treatment. All the test compounds were administered by oral gavage in a 0.5% carboxymethylcellulose suspension.

Anti-inflammatory Activity.

The carrageenan-induced paw edema test was used on groups of five rats. Sixty minutes after administering the test compound, 0.1 ml of a 1% carrageenan solution in saline was injected into the plantar surface of the right hind paw of each rat. Paw volume, as determinated by measuring the amount of water displaced after immersing the paw up to the lateral malleolus level, was recorded immediately after the carrageenan injection and again 3 hours later. The difference between these two values was taken as edema volume. The inhibition percentage of the edema of treated rats with respect to controls was calculated and compared to that which was produced by indomethacin (5 and 10 mg/kg).

Analgesic Activity.

The writhing test was used on a group of six mice. One hour after the administration of the test compound, 0.01 ml/g of a 0.6% acetic acid solution was injected intraperitoneally in each mouse. The writhing movements of each animal were counted for 10 minutes (between the 5th and 15th minute after the injection of the irritant). The analgesic effect was expressed as the percentage of protection compared with the control group. Dypirone (200 mg/kg) was used as a reference standard.

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