Reaction of 2-Dimethylaminomethylene-1,3-diones with Dinucleophiles. VI. Synthesis of Ethyl or Methyl 1,5-Disubstituted 1*H*-Pyrazole-4-carboxylates

Giulia Menozzi, Luisa Mosti and Pietro Schenone*,

Istituto di Scienze Farmaceutiche dell'Università, Viale Benedetto XV, 3,
16132 Genova, Italy

Received April 20, 1987

Reaction of ethyl or methyl 3-oxoalkanoates with *N,N*-dimethylformamide dimethyl acetal gave, generally in excellent yields, a series of ethyl or methyl 2-dimethylaminomethylene-3-oxoalkanoates **II** which reacted with phenylhydrazine to afford the esters of 5-substituted 1-phenyl-1*H*-pyrazole-4-carboxylic acids **III** in high yields. Esters **III** were hydrolyzed to the relative 5-substituted 1-phenyl-1*H*-pyrazole-4-carboxylic acids which were converted by heating to 5-substituted 1-phenyl-1*H*-pyrazoles in excellent yields. Reaction of **II** with methylhydrazine afforded in general a mixture of 3- and 5-substituted ethyl 1-methyl-1*H*-pyrazole-4-carboxylates with the exception of **IIg**, which gave in high yield methyl 5-benzyl-1-methyl-1*H*-pyrazole-4-carboxylate, which was hydrolyzed to the relative pyrazolecarboxylic acid. This afforded by heating 5-benzyl-1-methyl-1*H*-pyrazole in quantitative yield.

J. Heterocyclic Chem., **24**, 1669 (1987).

In the preceding papers of the series [1-5] we reported the facile reaction of open-chain *sym*-2-dimethylaminomethylene-1,3-diones with various dinucleophiles to give functionalyzed pyrazoles, isoxazoles, pyrimidines and pyridines.

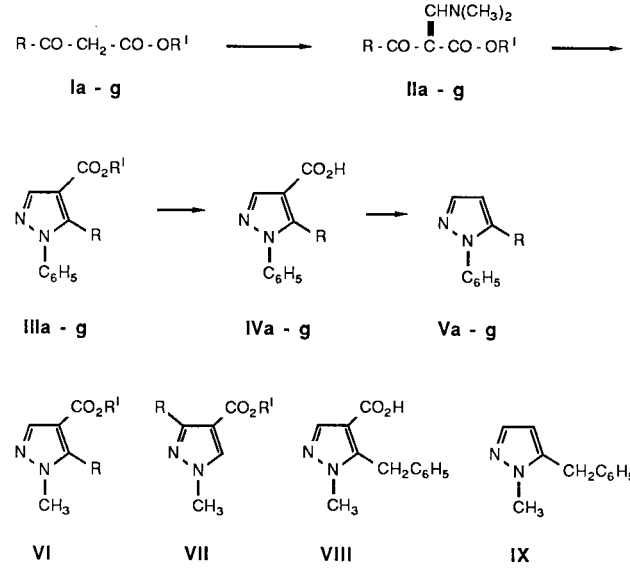
Provided that the first step of these reactions is the attack of the more reactive site of the dinucleophile on the highly electrophilic extra-chain carbon atom of the synthon [1], there were no problems concerning the regiospecificity of the cyclization step *via* interaction of a carbonyl group with the other nucleophilic site, owing to the symmetrical nature of the 1,3-dione.

We reasoned that other 2-dimethylaminomethylene-1,3-diones, although unsymmetrical, could be fruitfully employed in the reaction with dinucleophiles, only if one of the two carbonyl groups showed a markedly stronger electrophilicity in comparison with the other; in this case, the cyclization step could still be regiospecific.

This opportunity appeared practicable with 2-dimethylaminomethylene-3-oxoalkanoic esters **II**, since it is well known that a ketone carbonyl group is decidedly more electrophilic than an ester carbonyl group.

Once more (*cf* [1]), esters of 2-ethoxymethylene-3-oxoalkanoic acids were in some instances employed in the past in the reaction with dinucleophiles such as phenylhydrazine [6,7] and methylhydrazine [8] to afford only with the former dinucleophile the esters of 5-substituted-1-phenyl-1*H*-pyrazole-4-carboxylic acids **IIIa,f** in a regiospecific manner.

We wish to report now the use of esters of 2-dimethylaminomethylene-3-oxoalkanoic acids **II** in the reaction with *N,N*-dinucleophiles such as phenylhydrazine and methylhydrazine for the synthesis of esters of 5-substituted (1-phenyl)(1-methyl)-1*H*-pyrazole-4-carboxylic acids **III** and **VI**.

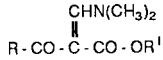


	R	R'
a	CH_3	C_2H_5
b	C_2H_5	C_2H_5
c	$(CH_2)_2CH_3$	C_2H_5
d	$CH(CH_3)_2$	C_2H_5
e	$C(CH_3)_3$	C_2H_5
f	C_6H_5	C_2H_5
g	$CH_2C_6H_5$	CH_3

As in the case of *sym*-2-dimethylaminomethylene-1,3-diones [1] we prepared, generally in excellent yields, the synthons **IIa-f** (Table I) by refluxing a solution of ethyl or methyl 3-oxoalkanoates **Ia-g** in *N,N*-dimethylformamide dimethyl acetal (in the case of **IIg** the reaction was carried out at 0°). To our knowledge, the same procedure was also

Table I

Esters of 2-Dimethylaminomethylene-3-oxoalkanoic Acids **IIa-g**



Formula Number	R	R'	Reflux Time (hours)	Yield %	Bp/mm or Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	CH_3	C_2H_5	1	91	110-112/0.5 [a]	$C_9H_{15}NO_3$	58.36 58.06	8.16 8.23	7.56 7.51
IIb	C_2H_5	C_2H_5	1	96	118-120/0.5	$C_{10}H_{17}NO_3$	60.28 60.02	8.60 8.68	7.03 6.89
IIc	$(CH_2)_2CH_3$	C_2H_5	1	95	112-115/0.5	$C_{11}H_{19}NO_3$	61.95 61.65	8.98 9.00	6.57 6.59
IId	$CH(CH_3)_2$	C_2H_5	1	92	112-115/0.5	$C_{11}H_{19}NO_3$	61.95 61.72	8.98 9.11	6.57 6.40
IIe	$C(CH_3)_3$	C_2H_5	4	60	108-110/0.5 48 [b]	$C_{12}H_{21}NO_3$	63.41 63.47	9.31 9.27	6.16 6.12
IIf	C_6H_5	C_2H_5	1	94	150-155/0.5 62 [c]	$C_{14}H_{17}NO_3$	68.00 68.06	6.93 7.04	5.66 5.67
IIg	$CH_2C_6H_5$	CH_3	[d]	74	145-150/0.15	$C_{14}H_{17}NO_3$	68.00 67.70	6.93 6.94	5.66 5.40

[a] Reference [10], bp 180-182°/15, 77% yield. [b] From petroleum ether bp 40-70°. [c] From anhydrous diethyl ether-petroleum ether 1:1. Reference [11], mp 63-65°, 91% yield. [d] One hour at room temperature.

Table II

UV, IR and NMR Spectral Data of Compounds **IIa-g**

Compound	UV, λ max nm (log ε)	IR, cm^{-1}	NMR, δ
IIa	248 (3.87) 304 (3.99)	1690, 1645, 1573	1.25 (mc, CH_3), 2.26 and 2.33 (2 s, CH_3CO), 3.00 and 3.06 [2 s, $(CH_3)_2N$], 4.17 (mc, CH_2O), 7.62 and 7.70 (2 s, =CHN) [a]
IIb	252 (3.88) 305 (4.04)	1685, 1645, 1575	1.10 (t, J = 6.5, C-ethyl CH_3), 1.31 (t, J = 6.5, O-ethyl CH_3), 2.68 (q, J = 6.5, CH_2), 3.04 [s, $(CH_3)_2N$], 4.24 (q, J = 6.5, CH_2O), 7.67 (s, =CHN)
IIc	252 (3.89) 305 (4.07)	1680, 1643, 1574	0.92 (t, J = 7.2, propyl CH_3), 1.30 (t, J = 7.2, O-ethyl CH_3), 1.54 (mc, propyl CH_2), 2.62 (t, J = 7.2, propyl CH_2), 3.02 [s, $(CH_3)_2N$], 4.22 (q, J = 7.2, CH_2O), 7.65 (s, =CHN)
IId	254.5 (3.81) 303 (3.97)	1678, 1645, 1575	1.08 [d, J = 7.2, $(CH_3)_2C$], 1.29 (t, J = 7.2, ethyl CH_3), 2.7-3.6 (m, $CHMe_2$), 3.01 and 3.11 [2 s, $(CH_3)_2N$], 4.22 (q, J = 7.2, CH_2O), 7.62 and 7.73 (2 s, =CHN) [a]
IIe	270.5 (4.18) 282 sh (4.14)	1695, 1643, 1598	1.22 [mc, $(CH_3)_3C$ + ethyl CH_3), 2.89 [s, $(CH_3)_2N$], 4.18 (q, J = 7, CH_2O), 7.37 (s, =CHN) [b]
IIf	255 (4.13) 273 (4.17) 313 (3.91)	1682, 1633, 1602	0.90 (t, J = 7, CH_3), 2.98 [s, $(CH_3)_2N$], 3.96 (q, J = 7, CH_2O), 7.48 (mc, 2 H ar *m* + 1 H ar *p*), 7.71 (mc, 2 H ar *o* + =CHN)
IIg	254 (3.90) 313 (4.09)	1690, 1640, 1573	2.89 [s, $(CH_3)_2N$], 3.72 (s, CH_3O), 4.02 (s, CH_2), 7.25 (s, C_6H_5), 7.67 (s, =CHN)

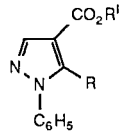
[a] Mixture of *E* and *Z* isomers. [b] Reference [11], δ 1.0 (t), 3.0 (s), 3.9 (q), 7.5 (m).

applied to some γ,δ-unsaturated β-ketoesters to give crude α-dimethylaminomethylene derivatives which however were not characterized [9]. Only two compounds **II** are known, namely **IIa** (prepared from ethyl acetoacetate and *N,N*-dimethylformamide diethyl acetal [10]), and **IIf** [11].

Synthons **IIa** and **IId** are a mixture of *E* and *Z* isomers, as can be seen from the presence in their nmr spectra of two singlets for $N(CH_3)_2$ and =CH groups (Table II).

Table III

Esters of 5-Substituted 1-Phenyl-1*H*-pyrazole-4-carboxylic Acids **IIIa-g**



Formula Number	R	R'	Yield %	Bp/mm or Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	CH_3	C_2H_5	96	108-110/0.15 49 [a] [b]	$C_{13}H_{14}N_2O_2$	67.81 67.72	6.13 6.28	12.17 12.09
IIIb	C_2H_5	C_2H_5	89	97-100/0.1 [c]	$C_{14}H_{16}N_2O_2$	68.83 68.62	6.60 6.86	11.47 11.68
IIIc	$(CH_2)_2CH_3$	C_2H_5	95	110-115/0.3	$C_{15}H_{18}N_2O_2$	69.74 69.82	7.02 7.14	10.84 11.00
IIId	$CH(CH_3)_2$	C_2H_5	93	100-105/0.2 49 [a]	$C_{15}H_{18}N_2O_2$	69.74 69.76	7.02 7.26	10.84 10.99
IIIe	$C(CH_3)_3$	C_2H_5	68	115-117/0.15 63 [d]	$C_{16}H_{20}N_2O_2$	70.56 70.73	7.40 7.44	10.29 10.30
IIIf	C_6H_5	C_2H_5	83	113 [e] [f]	$C_{18}H_{16}N_2O_2$	73.95 73.86	5.52 5.61	9.58 9.42
IIIg	$CH_2C_6H_5$	CH_3	87	98 [g]	$C_{18}H_{16}N_2O_2$	73.95 73.99	5.52 5.51	9.58 9.60

[a] From petroleum ether. [b] Reference [6], mp 55-56°. [c] Reference [12], bp 170-172°/1.5, 89% yield. [d] From hexane. [e] From 95% ethanol. [f] Reference [7], mp 112.5-114°; reference [16], mp 116°, 31% yield; reference [17], mp 116-118°, 16% yield. [g] From diethyl ether.

Table IV

UV, IR and NMR Spectral Data of Compounds **IIIa-g**

Compound	UV, λ max nm (log ε)	IR, cm^{-1}	NMR, δ
IIIa	237 (4.17)	1707, 1602, 1562, 1505	1.35 (t, J = 7.2, ethyl CH_3), 2.56 (s, CH_3-5), 4.33 (q, J = 7.2, CH_2O), 7.47 (s, C_6H_5), 8.05 (s, CH-3)
IIIb	233 (4.16)	1707, 1602, 1557, 1505	1.17 (t, J = 7.2, 5-ethyl CH_3), 1.37 (t, J = 7.2, O-ethyl CH_3), 2.98 (q, J = 7.2, CH_2-5), 4.35 (q, J = 7.2, CH_2O), 7.50 (s, C_6H_5), 8.07 (s, CH-3) [a]
IIIc	233.5 (4.17)	1705, 1600, 1553, 1503	0.85 (t, J = 7.2, propyl CH_3), 1.15-1.95 (m, propyl CH_2), 1.36 (t, J = 7.2, ethyl CH_3), 2.96 (near t, J = 7.5, propyl CH_2), 4.34 (q, J = 7.2, CH_2O), 7.48 (s, C_6H_5), 8.06 (s, CH-3)
IIId	232 (4.16)	1713, 1600, 1548, 1503	1.36 [d, J = 7.2, $(CH_3)_2C$], 1.37 (t, J = 6.6, ethyl CH_3), 3.30 (mc, $CHMe_2$), 4.33 (q, J = 6.6, CH_2O), 7.47 (s, C_6H_5), 8.07 (s, CH-3)
IIIe	232.5 (4.105)	1713, 1600, 1523, 1500	1.31 [s, $(CH_3)_3C$], 1.35 (t, J = 7.2, ethyl CH_3), 4.31 (q, J = 7.2, CH_2O), 7.41 (mc, C_6H_5), 7.97 (s, CH-3)
IIIf	248 (4.20)	1710, 1600, 1553, 1503	1.21 (t, J = 6.6, CH_3), 4.23 (q, J = 6.6, CH_2O), 7.27 (s, C_6H_5), 7.35 (s, C_6H_5), 8.22 (s, CH-3)
IIIg	234.5 (4.18)	1711, 1600, 1555, 1503	3.82 (s, CH_3O), 4.38 (s, CH_2), 6.8-7.6 (m, 2 C_6H_5), 8.11 (s, CH-3)

[a] Reference [12], δ 1.16 (t, J = 7), 1.38 (t, J = 7), 2.95 (q, J = 7), 4.33 (q, J = 7), 7.45 (s), 8.05 (s).

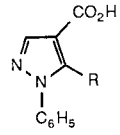
The reactions of **IIa-g** with phenylhydrazine were carried out in refluxing anhydrous ethanol (1-butanol for **IIe**) to give in 83-96% yields the esters of 5-substituted 1-phenyl-1*H*-pyrazole-4-carboxylic acids **IIIa-d,f,g** (Table III) as sole products.

Also in the case of **IIe**, whose carbonyl group is strongly hindered by the bulky *t*-butyl group, the ester **IIIe** was obtained as a sole product in 68% yield.

The structure of esters **IIIa,f** was proven by comparison with the products obtained from esters of 2-ethoxymethyl-

Table V

5-Substituted 1-Phenyl-1*H*-pyrazole-4-carboxylic Acids **IVa-g**



Formula Number	R	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IVa	CH_3	92	169 [a] [b]	$C_{11}H_{10}N_2O_2$	65.34 65.36	4.98 5.06	13.85 13.87
IVb	C_2H_5	86	163 [a]	$C_{12}H_{12}N_2O_2$	66.65 66.72	5.59 5.65	12.95 12.90
IVc	$(CH_2)_2CH_3$	82	112 [c]	$C_{13}H_{14}N_2O_2$	67.81 67.85	6.13 6.23	12.17 12.06
IVd	$CH(CH_3)_2$	94	168 [a]	$C_{13}H_{14}N_2O_2$	67.81 67.69	6.13 6.00	12.17 12.10
IVe	$C(CH_3)_3$	79	179 [a]	$C_{14}H_{16}N_2O_2$	68.83 68.53	6.60 6.54	11.47 11.30
IVf	C_6H_5	100	183 [a] [d]	$C_{16}H_{12}N_2O_2$	72.72 72.52	4.58 4.70	10.60 10.54
IVg	$CH_2C_6H_5$	92	159 [a]	$C_{17}H_{14}N_2O_2$	73.37 73.37	5.07 5.09	10.06 10.04

[a] From anhydrous diethyl ether. [b] Reference [6], mp 167-168°. [c] From anhydrous diethyl ether-petroleum ether 1:1. [d] Reference [7], mp 180°.

Table VI

UV, IR and NMR Spectral Data of Compounds **IVa-g**

Compound	UV, λ max nm (log ε)	IR, cm^{-1}	NMR, δ
IVa	239 (4.07)	3600-2400, 1676, 1600, 1560, 1500	2.58 (s, CH_3), 7.48 (s, C_6H_5), 8.12 (s, CH-3), 11.79 (s, CO_2H, disappears with deuterium oxide)
IVb	232.5 (4.10)	3600-2400, 1677, 1600, 1552, 1500	1.18 (t, J = 7.2, CH_3), 2.97 (q, J = 7.2, CH_2), 7.48 (s, C_6H_5), 8.12 (s, CH-3), 11.97 (s, CO_2H, disappears with deuterium oxide)
IVc	232.5 (4.11)	3600-2400, 1677, 1600, 1550, 1500	0.85 (t, J = 7.2, CH_3), 1.53 (mc, CH_2), 2.99 (mc, CH_2), 7.51 (s, C_6H_5), 8.16 (s, CH-3), 11.86 (s, CO_2H, disappears with deuterium oxide)
IVd	230.5 (4.09)	3600-2300, 1685, 1600, 1545, 1502	1.38 [d, J = 7.2, $(CH_3)_2C$], 3.33 (mc, $CHMe_2$), 7.48 (s, C_6H_5), 8.15 (s, CH-3), 11.66 (s, CO_2H, disappears with deuterium oxide)
IVe	230 (3.985)	3600-2300, 1693, 1600, 1523, 1500	1.33 [s, $(CH_3)_3C$], 7.43 (s, C_6H_5), 8.12 (s, CH-3), 11.47 (s, CO_2H, disappears with deuterium oxide)
IVf	249 (4.175)	3600-2300, 1690, 1600, 1553, 1500	7.23 (s, C_6H_5), 7.30 (s, C_6H_5), 8.23 (s, CH-3), 11.28 (s, CO_2H, disappears with deuterium oxide)
IVg	234 (4.08)	3600-2400, 1677, 1598, 1550, 1497	4.39 (s, CH_2), 6.8-7.7 (m, 2 C_6H_5), 8.19 (s, CH-3), 11.55 (s, CO_2H, disappears with deuterium oxide)

ene-3-oxoalkanoic acids (see above), and for these and the remaining compounds **III** by conversion to 5-substituted 1-phenyl-1*H*-pyrazoles **V** (see later).

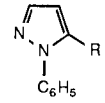
On the other hand, the nmr spectral data of esters **III** (Table IV) were in agreement with the proposed structures.

The ester **IIIb** was the sole product described in the literature which was prepared by this method, starting from the crude synthon **IIb** not isolated [12].

Esters **IIIa-g** were converted to the corresponding 5-substituted 1-phenyl-1*H*-pyrazole-4-carboxylic acids **IVa-g** (Table V) by saponification with potassium hydrox-

Table VII

5-Substituted 1-Phenyl-1*H*-pyrazoles **Va-g**



Formula Number	R	Heating Time (hours)	Yield %	Bp/mm or Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
Va	CH_3	36 [a]	98	65-70/0.2 [c]	$C_{10}H_{10}N_2$	75.92 75.72	6.37 6.42	17.71 17.56
Vb	C_2H_5	16 [a]	100	75-80/0.2	$C_{11}H_{12}N_2$	76.71 76.47	7.02 7.06	16.26 16.47
Vc	$(CH_2)_2CH_3$	36 [a]	91	85-90/0.2 [d]	$C_{12}H_{14}N_2$	77.38 77.08	7.58 7.74	15.04 15.33
Vd	$CH(CH_3)_2$	12 [a]	98	70-75/0.2 [e]	$C_{12}H_{14}N_2$	77.38 77.13	7.58 7.54	15.04 15.15
Ve	$C(CH_3)_3$	5 [a]	97	85-90/0.2 74 [f]	$C_{13}H_{16}N_2$	77.96 78.08	8.05 8.10	13.99 14.13
Vf	C_6H_5	26 [b]	96	115-120/0.2 53 [f] [g]	$C_{15}H_{12}N_2$	81.79 81.89	5.49 5.45	12.72 13.01
Vg	$CH_2C_6H_5$	25 [a]	84	130-135/0.2	$C_{16}H_{14}N_2$	82.02 81.77	6.02 5.98	11.96 11.96

[a] Heating temperature, 200°. [b] Heating temperature, 210°. [c] Reference [18], bp 87-88°/0.9. [d] Reference [19], bp 156°/15. [e] Reference [20], bp 145-150°/15. [f] From petroleum ether. [g] Reference [21], mp 55-56°, bp 167°/12.

Table VIII

UV, IR and NMR Spectral Data of Compounds **Va-g**

Compound	UV, λ max nm (log ε)	IR, cm^{-1}	NMR, δ
Va	239 (4.01)	1601, 1543, 1501, 1453, 1393	2.33 (s, CH_3), 6.18 (d, J = 1.6, CH-4), 7.42 (mc, C_6H_5), 7.56 (d, J = 1.6, CH-3) [a]
Vb	237.5 (3.99)	1600, 1533, 1500, 1467, 1453, 1398	1.19 (t, J = 7.2, CH_3), 2.66 (q, J = 7.2, CH_2), 6.22 (d, J = 1.6, CH-4), 7.41 (mc, C_6H_5), 7.58 (d, J = 1.6, CH-3)
Vc	236.5 (3.985)	1600, 1530, 1500, 1453, 1395	0.39 (t, J = 7.2, CH_3), 1.58 (near sex, J = 7.2, CH_2), 2.62 (t, J = 7.2, CH_2), 6.20 (d, J = 1.5, CH-4), 7.42 (s, C_6H_5), 7.58 (d, J = 1.5, CH-3)
Vd	234 (3.92)	1598, 1528, 1500, 1452, 1395	1.18 [d, J = 6, $(CH_3)_2C$], 3.07 (mc, $CHMe_2$), 6.21 (d, J = 1.8, CH-4), 7.44 (s, C_6H_5), 7.58 (d, J = 1.8, CH-3)
Ve	221 sh (3.85)	1600, 1502, 1478, 1454, 1385	1.18 [s, $(CH_3)_3C$], 6.18 (d, J = 1.8, CH-4), 7.41 (s, C_6H_5), 7.50 (d, J = 1.8, CH-3)
Vf	248 (4.22)	1600, 1504, 1453, 1442, 1390	6.47 (d, J = 1.6, CH-4), 7.24 (s, C_6H_5), 7.29 (s, C_6H_5), 7.69 (d, J = 1.6, CH-3) [b]
Vg	235 (3.99)	1600, 1530, 1500, 1452, 1397	3.99 (s, CH_2), 6.12 (2 t, J′ = 1.8, J″ = 0.6, CH-4), 7.18 (mc, C_6H_5), 7.36 (s, C_6H_5), 7.59 (d, J = 1.8, CH-3)

[a] Reference [22], δ 2.34 (s), 6.19 (d, J = 1.5), 7.43 (s), 7.56 (d, J = 1.5). [b] Reference [23], δ 6.50 (d, J = 1.6), 7.24 (s), 7.30 (s), 7.64 (d, J = 1.6).

ide in boiling ethanol followed by acidification, in 79-100% yields. The ir and nmr spectral data (Table VI) were in agreement with the proposed structures.

Finally, decarboxylation of acids **IVa-g** by simply heating at temperatures above their melting points afforded 5-substituted 1-phenyl-1*H*-pyrazoles **Va-g** (Table VII) in 84-100% yields.

Some of these pyrazoles, prepared by other routes, where already known; therefore, the identity of their ir and nmr spectral data with those of our compounds unequivocally established the structures of pyrazoles **V** and consequently also those of the starting esters **III**.

The above cyclization clearly is depending on the strong difference of nucleophilicity between the NHPh and NH_2 groups of phenylhydrazine, the latter being the most nucleophilic [13] and the sole to react with the highly electrophilic extra-chain carbon atom of **II**.

With methylhydrazine the situation is more complicated, this dinucleophile reacting to a large extent also *via* its $NHCH_3$ group, whose nucleophilicity is perhaps superior to that of the NH_2 group [13]. In fact, the reaction of ethyl 2-ethoxymethyleneacetoacetate with methylhydrazine in diethyl ether gave ester **VIIa** containing 5-10% of the isomer **VIa** [8]. We have repeated this reaction with ethyl 2-dimethylaminomethyleneacetoacetate **IIa** both in diethyl ether and in methanol solution; in the former case, a mixture of esters **VIIa/VIa** in a ratio of 76/24 was obtained, whereas in the latter case the composition of the mixture was nearly reversed, the ratio being 23/77.

Thus, in the reaction of **IIa** with methylhydrazine the composition of isomers mixture appears to be strongly dependent on the solvent employed.

The reaction of **IIb-f** with methylhydrazine was therefore carried out in methanol solution in the hope of obtaining a clear prevalence of 1,5-disubstituted esters **VI**, but only unseparable mixtures of esters **VIb-f** and **VIIb-f** as liquids which easily distilled *in vacuo* were always obtained.

Only synthon **IIg** gave as unique product the ester **VIg** in high yield, whose structure was proven by conversion to 5-benzyl-1-methyl-1*H*-pyrazole-4-carboxylic acid **VIII** in excellent yield, from which 5-benzyl-1-methyl-1*H*-pyrazole **IX** was obtained in quantitative yield. The structure of pyrazole **IX** was proven by comparison of nmr spectral data of C-3 and C-4 protons with those of 1,5- and 1,3-dimethylpyrazole [14] (see Experimental).

In conclusion, the reaction of esters of 2-dimethylaminomethylene-3-oxoalkanoic acids with phenylhydrazine seems to offer another useful synthetic pathway to functionalized pyrazoles, whose pharmacological interest is well known [15].

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Perkin-Elmer Model 550S spectrophotometer. The ir spectra were taken in chloroform on a Perkin-Elmer Model 398 spectrophotometer, and the nmr spectra were recorded in deuteriochloroform on Perkin-Elmer Model R-600 (60 MHz) and Varian Model FT-80 (80 MHz) instruments (TMS as internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus.

General Procedure for Esters of 2-Dimethylaminomethylene-3-oxoalkanoic Acids **IIa-g**.

A solution of 3-oxoalkanoic acid ethyl or methyl ester **Ia-g** (0.10 moles) in *N,N*-dimethylformamide dimethyl acetal (14.3 g, 0.12 mole) was stirred at room temperature for 1 hour (**Ig**) or refluxed for a certain time (Table I). The excess acetal was distilled off under reduced pressure and the orange residue was purified by bulb-to-bulb distillation *in vacuo*. Compounds **Ie,f**, which became solid after distillation, were further purified by recrystallization from a suitable solvent.

General Procedure for Esters of 5-Substituted 1-Phenyl-1*H*-pyrazole-4-carboxylic Acids **IIIa-g**.

Phenylhydrazine (1.14 g, 10.5 mmoles) in anhydrous ethanol (1-butanol for **IIe**) (20 ml) was slowly added with stirring to a solution of **II** (10 mmoles) in anhydrous ethanol (1-butanol for **IIe**) (20 ml). The resulting solution was refluxed for 2 hours and evaporated under reduced pressure. The residue was treated with water (30 ml) and extracted twice with chloroform. The chloroform extracts were washed with a saturated solution of sodium hydrogen carbonate and with water, dried (magnesium sulfate) and evaporated under reduced pressure to give a residue which was purified by recrystallization from a suitable solvent (**IIIf,g**) or by distillation *in vacuo*. Before distillation, compounds **IIId,e** were chromatographed of Florisil, using diethyl ether as eluant. Compounds **IIIa,d,e** became solid after distillation and were further purified by recrystallization from a suitable solvent (Table III).

General Procedure for 5-Substituted 1-Phenyl-1*H*-pyrazole-4-carboxylic Acids **IVa-g**.

Potassium hydroxide (1.68 g, 30 mmoles) dissolved in 95% ethanol (10 ml) was added to a solution of **III** (10 mmoles) in the same solvent (10 ml). The resulting solution was refluxed with stirring for 5 hours, the solvent was evaporated under reduced pressure and the residue was dissolved with water (50 ml). The aqueous solution was acidified with 6*N* hydrochloric acid (*p*H ~ 1) and the white solid which separated was extracted thoroughly with chloroform. The chloroform extracts were dried (magnesium sulfate) and evaporated under reduced pressure to give residues which were purified by recrystallization from a suitable solvent (Table V).

General Procedure for 5-Substituted 1-Phenyl-1*H*-pyrazoles **Va-g**.

Acids **IVa-g** (about 10 mmoles) were decarboxylated by heating at temperatures above their melting points for a certain time (Table VII), until the evolution of carbon dioxide subsided. From time to time the decarboxylated product was distilled *in vacuo* during the heating, and the collected distillates were further purified by distillation. Pyrazoles **Va,f** solidified after distillation and were recrystallized from a suitable solvent.

Reaction of **IIa** with Methylhydrazine.

a) Methylhydrazine (0.51 g, 11 mmoles) in dry methanol (20 ml) was slowly added with stirring to a solution of **IIa** (1.85 g, 10 mmoles) in dry methanol (30 ml). The resulting solution was stirred at 0° for 15 minutes and at room temperature for 1 hour. The solution was evaporated under reduced pressure and the yellow oily residue was distilled *in vacuo*, bp 60-65°/0.15, yield, 1.47 g (88%); nmr (deuteriochloroform): δ 1.33 (t, J = 7.2, ethyl CH_3), 2.45 and 2.54 (2 s, CH_3), 3.81 (near s, CH_3N), 4.28 (q, J = 7.2, CH_2), 7.83 (near s, =CH).

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 56.94; H, 7.15; N, 16.83.

From the nmr methyl signals, a mixture **VIIa/VIa** in a ratio 23/77 was calculated.

b) When the reaction was carried out as above, but using anhydrous diethyl ether as the solvent, a yellow waxy solid was obtained which was distilled *in vacuo* to give a liquid, bp 60-65°/0.1, which soon solidified (1.3 g, 77%). Recrystallization from anhydrous diethyl ether afforded a solid mp 50-55° with a nmr spectrum as above, from which a mixture of **VIIa/VIa** in a ratio 76/24 was calculated. By further recrystallizations from petroleum ether, ester **VIIa** could be obtained pure, mp 55-56°; nmr (deuteriochloroform): δ 1.33 (t, J = 7.2, ethyl CH_3), 2.47 (s, CH_3-3), 3.86 (s, CH_3N), 4.29 (q, J = 7.2, CH_2), 7.82 (s, =CH) [Reference [8], mp 58-59°, nmr (deuteriochloroform): δ 1.34 (t), 2.46 (s), 3.85 (s), 4.30 (q), 7.83 (s). Ester **VIa**: bp 78-80°/0.05; nmr (deuteriochloroform): δ 1.34 (t), 2.55 (s), 3.80 (s), 4.30 (q), 7.83 (s)].

Reaction of **IIb-g** with Methylhydrazine.

When the reaction of **IIb-f** with methylhydrazine was carried out in methanol solution according to the above procedure a), unseparable mixture of esters **VI** and **VII** were always obtained (91-98% yields) as liquids easily distillable under 70° at 0.1 mm, which showed correct elemental analyses for C, H, N. The presence of two isomers was inferred from two signals for C-ethyl CH_2 group (**IIb**) or for NCH_3 group (**IIc,d,e,f**). In some instances (**IIe,f**), also the singlets of both H-3 and H-5 were present. Only **IIg** gave as unique product the ester **VIg** (89% yield) as a solid, mp 100° from diethyl ether; uv: λ max nm (log ε) 225 (4.09); ir (chloroform): ν max 1709, 1605, 1555, 1495 cm^{-1}; nmr (deuteriochloroform): δ 3.69 (s, CH_3N), 3.81 (s, CH_3O), 4.41 (s, CH_2), 7.22 (mc, C_6H_5), 7.90 (s, CH-3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.82; H, 6.24; N, 12.09.

5-Benzyl-1-methyl-1*H*-pyrazole-4-carboxylic Acid **VIII**.

This acid was obtained in 92% yield according to the general procedure described for acids **IV**, mp 202° from ethyl acetate; uv: λ max nm (log ε) 216 sh (4.065); ir (potassium bromide): ν max 3300-2100, 1675, 1600, 1535, 1490 cm^{-1}; nmr (DMSO-d_6): δ 3.69 (s, CH_3), 4.43 (s, CH_2), 7.25 (s, C_6H_5), 7.83 (s, CH-3), ~11 (very broad s, 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, 66.74; H, 5.58; N, 13.02.

5-Benzyl-1-methyl-1*H*-pyrazole **IX**.

This pyrazole was obtained in 100% yield following the general procedure described for pyrazoles **V**, heating at 250° for 3 hours; slightly yellow liquid, bp 85-90°/0.2; uv: λ max nm (log ε) 258 (3.12); ir (chloroform): ν max 1608, 1538, 1497, 1485, 1457 cm^{-1}; nmr (deuteriochloroform): δ 3.66 (s, CH_3), 3.95 (s, CH_2), 5.99 (d, J = 1.8, CH-4), 7.22 (mc, C_6H_5), 7.38 (d, J = 1.8, CH-3).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.43; H, 7.08; N, 16.53.

1,5-Dimethylpyrazole shows CH-3 and CH-4 doublets at δ 7.36 and 5.98, J = 2.0; 1,3-dimethylpyrazole, CH-5 and CH-4 doublets at δ 7.22 and 5.95, J = 2.0 [14].

Acknowledgements.

The authors wish to thank Mr. A. Panaro for the microanalyses and Mr. F. Fasce and C. Rossi for the uv, ir and nmr spectra. Financial support for CNR, Rome, is gratefully acknowledged.

REFERENCES AND NOTES

[1] P. Schenone, L. Mosti and G. Menozzi, *J. Heterocyclic Chem.*, **19**, 1355 (1982).

[2] G. Menozzi, P. Schenone and L. Mosti, *J. Heterocyclic Chem.*, **20**, 645 (1983).

[3] L. Mosti, G. Menozzi and P. Schenone, *J. Heterocyclic Chem.*, **20**, 649 (1983).

[4] G. Menozzi, L. Mosti and P. Schenone, *J. Heterocyclic Chem.*, **21**, 1437 (1984).

[5] L. Mosti, P. Schenone and G. Menozzi, *J. Heterocyclic Chem.*, **22**, 1503 (1985).

[6] L. Claisen, *Ann. Chem.*, **295**, 301 (1897).

[7] L. Panizzi, *Gazz. Chim. Ital.*, **73**, 13 (1943).

[8] J. L. Huppatz, *Aust. J. Chem.*, **36**, 135 (1983).

[9] S. Gelin and C. Deshayes, *Synthesis*, 566 (1983).

[10] H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann. Chem.*, **641**, 1 (1961).

[11] E. J. Breaux and K. E. Zwikelmaier, *J. Heterocyclic Chem.*, **18**, 183 (1981).

[12] M. Albrand and S. Gelin, *Synthesis*, 1030 (1983).

[13] G. Coispeau, J. Elguero and R. Jacquier, *Bull. Soc. Chim. France*, 689 (1970).

[14] J. Elguero, "Pyrazoles and their Benzo Derivatives", in "Comprehensive Heterocyclic Chemistry", Vol **5**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, p 186.

[15] Reference [14], p 291.

[16] G. Scherowsky and H. Franke, *Tetrahedron Letters*, 1673 (1974).

[17] M. T. Bergeon, C. Metayer, and H. Quiniou, *Bull. Soc. Chim. France*, 917 (1971).

[18] R. G. Micetich, V. Baker, P. Spevak, T. W. Hall, and B. K. Bains, *Heterocycles*, **23**, 943 (1985).

[19] E. Benary, *Ber.*, **59**, 2198 (1926).

[20] G. Bianchetti, D. Pocar, P. Dalla Croce, and A. Vigevani, *Chem. Ber.*, **98**, 2715 (1965).

[21] K. von Auwers and W. Schmidt, *Ber.*, **58**, 528 (1925).

[22] L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

[23] T. Rull and G. Le Strat, *Bull. Soc. Chim. France*, 1375 (1975).