Reaction of 2-Dimethylaminomethylene-1,3-diones with Dinucleophiles. X. Synthesis of 5-Substituted Ethyl or Methyl 4-Isoxazolecarboxylates and Methyl 4-(2,2-Dimethyl-1-oxopropyl)-5-isoxazolecarboxylate [1]

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Reaction of ethyl or methyl 2-dimethylaminomethylene-3-oxoalkanoates with hydroxylamine hydrochloride in methanol solution afforded in high yields the relative esters of 5-substituted 4-isoxazolecarboxylic acids **II**. These esters were hydrolyzed generally with concentrated hydrochloric acid-acetic acid mixtures to the corresponding carboxylic acids in satisfactory yields.

Ethyl or methyl esters **II** isomerized with sodium ethoxide or methoxide, respectively, to the corresponding esters or hemiesters of 2-cyano-3-oxoalkanoic acids generally in excellent to satisfactory yields.

Reaction of methyl 5,5-dimethyl-3-dimethylaminomethylene-2,4-dioxohexanoate with hydroxylamine hydrochloride afforded in moderate yield methyl 4-(2,2-dimethyl-1-oxopropyl)-5-isoxazolecarboxylate, which was converted by acid hydrolysis as above to 4-*t*-butyl-4-hydroxyfuro[3,4-*d*]isoxazol-6-(4*H*)-one.

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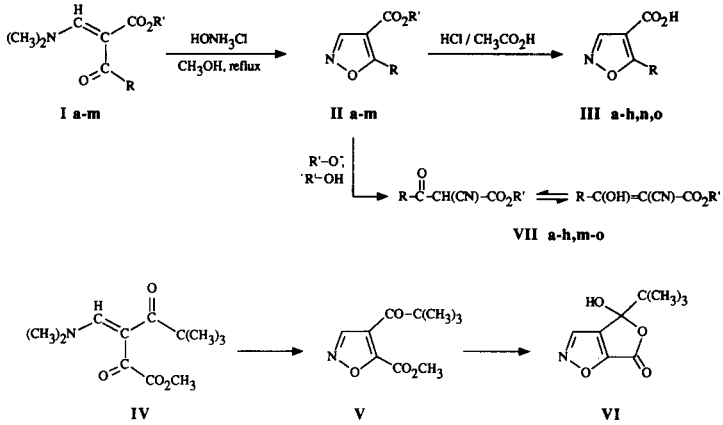
In previous papers of this series [2-4] some of us reported the efficient reaction of ethyl or methyl 2-dimethylaminomethylene-3-oxoalkanoates **Ia-h** with dinucleophiles such as phenylhydrazine, sodium cyanoacetamide and guanidine or amidines to give the corresponding esters of 5-substituted 1-phenyl-1*H*-pyrazole-4-carboxylic acids, 2-substituted 5-cyano-1,6-dihydro-6-oxo-3-pyridinecarboxylic acids and 2,4-disubstituted 5-pyrimidinecarboxylic acids, respectively. Later, the reaction with phenylhydrazine was extended successfully to the more complex synthons **Ii-m**, in which the alkane moiety R contained an ester group or was substituted by it, and to **IV**, a synthon having close to the reactive dimethylaminomethylene group two carbonyl groups with different reactivities [5].

As a consequence of the neat behavior of these synthons, which allowed *inter alia* the synthesis of heterocyclic derivatives with interesting pharmacological activities, and taking into account our former work on the reaction of open-chain *sym*-2-dimethylaminomethylene-1,3-diones with the simplest *N-O* dinucleophile, namely hydroxylamine, to give satisfactorily a series of 5-substituted 4-acylisoxazoles [6], we have now employed the unsymmetrical synthons **Ia-m** and **IV** in the reaction with hydroxylamine for the synthesis of 5-substituted ethyl or methyl 4-

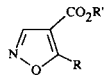


	R	R'
a	CH_3	C_2H_5
b	CH_2CH_3	C_2H_5
c	$(CH_2)_2CH_3$	C_2H_5
d	$CH(CH_3)_2$	C_2H_5
e	$C(CH_3)_3$	C_2H_5
f	$CH_2C_6H_5$	CH_3
g	C_6H_5	C_2H_5

	R	R'
h	CH_2OCH_3	CH_3
i	$(CH_2)_2CO_2CH_3$	CH_3
l	$(CH_2)_3CO_2C_2H_5$	C_2H_5
m	$CO_2C_2H_5$	C_2H_5
n	$(CH_2)_2CO_2H$	CH_3
o	$(CH_2)_3CO_2H$	C_2H_5

Table I

Esters of 5-Substituted 4-Isoxazolecarboxylic Acids **IIa-m**



Formula Number	R	R'	Yield %	Bp °C / mm or mp °C	Molecular Formula	Analyses % Calcd. / Found C	H	N
IIa	CH_3	C_2H_5	84	90-95 / 20 [a]	$C_7H_9NO_3$	54.19 54.18	5.85 5.89	9.03 9.35
IIb	CH_2CH_3	C_2H_5	76	90-95 / 14	$C_8H_{11}NO_3$	56.80 57.01	6.55 6.62	8.28 8.51
IIc	$(CH_2)_2CH_3$	C_2H_5	68	110-115 / 18	$C_9H_{13}NO_3$	59.00 59.23	7.15 7.21	7.64 7.68
IId	$CH(CH_3)_2$	C_2H_5	82	92-98 / 18	$C_9H_{13}NO_3$	59.00 59.21	7.15 7.25	7.64 7.50
IIe	$C(CH_3)_3$	C_2H_5	87	49-50 [b]	$C_{10}H_{15}NO_3$	60.90 60.86	7.66 7.75	7.10 7.38
IIf	$CH_2C_6H_5$	CH_3	74	120-125 / 0.3	$C_{12}H_{11}NO_3$	66.35 66.33	5.10 5.08	6.45 6.80
IIg	C_6H_5	C_2H_5	90	100-105 / 0.1 [c]	$C_{12}H_{11}NO_3$	66.35 66.56	5.10 5.18	6.45 6.53
IIh	CH_2OCH_3	CH_3	76	120-125 / 20	$C_7H_9NO_4$	49.12 48.98	5.30 5.38	8.18 8.34
IIi	$(CH_2)_2CO_2CH_3$	CH_3	85	95-100 / 0.1	$C_9H_{11}NO_5$	50.70 50.36	5.20 5.20	6.57 6.75
III	$(CH_2)_3CO_2C_2H_5$	C_2H_5	72	115-120 / 0.3	$C_{12}H_{17}NO_5$	56.46 56.19	6.71 6.76	5.49 5.65
IIm	$CO_2C_2H_5$	C_2H_5	70	85-90 / 0.3	$C_9H_{11}NO_5$	50.70 50.76	5.20 5.18	6.57 6.56

[a] Reference [7], bp 104° / 23, 60% yield. [b] From petroleum ether (bp 40-70°). [c] Reference [9], bp 142-143° / 4-5.

isoxazolecarboxylates **IIa-m** and methyl 4-(2,2-dimethyl-1-oxopropyl)-5-isoxazolecarboxylate **V**, respectively.

The reactions of **Ia-m** [2,5] with hydroxylamine were carried out by simply refluxing a methanol solution of the corresponding **I** and hydroxylamine hydrochloride (*cf.* [6]) to give in good yields 5-substituted ethyl or methyl 4-isoxazolecarboxylates **IIa-m** (Table I), whereas the reaction with **IV** gave ester **V** in moderate yield. It was not necessary to add a base in order to release hydroxylamine from its salt, since dimethylamine which is formed in the reaction probably acts in this way.

The structure of esters **IIa,g** was proved by comparison with the products obtained from esters of 2-ethoxymethylene-3-oxoalkanoic acids which, to our knowledge, were employed only in two cases in the reaction with hydroxylamine [7-9]; other evidence was provided by their conversion to carboxylic acids **IIIa,g** already known [7,9,10]. The ^{1}H nmr spectral data of esters **IIIa-m** (Table II) and **V** were in agreement with the proposed structures and demonstrated that a sole product was formed, with the exception of **IIa**, where a ratio of about 95/5 of **IIa** with respect to the isomer 3-methyl ester was calculated on the basis of 5-methyl and 3-methyl group singlets (see Experimental). However, a ratio of isomers even less favorable (90/10) was found in the products mixture obtained by repeating the reaction of Yasuda [7]. The structure of **V** was chiefly confirmed by the formation of lactone **VI** upon acid hydrolysis (see later). As in the case of the reaction of **IV** with phenylhydrazine [5], the formation of **V** could be explained by the decreased reactivity of 4-carbonyl group caused by steric hindrance, which forced the intermediate product resulting from the attack of hydroxylamine nitrogen to the strong electrophilic dimethylaminomethylene group to cyclize on 2-carbonyl group.

Table II

IR and ^{1}H NMR Spectral Data of Compounds **IIa-m**

Compound	IR, cm^{-1}	^{1}H NMR, δ
IIa	1720, 1613, 1483, 1420, 1384	1.35 (t, J = 7, 3H, Et CH_3), 2.70 (s, 3H, CH_3-5), 4.33 (q, J = 7, 2H, CH_2), 8.50 (s, 1H, H-3)
IIb	1717, 1608, 1483, 1420, 1380	1.33 (t, J = 7, 3H, 5-Et CH_3), 1.35 (t, J = 7, 3H, O-Et CH_3), 3.14 (q, J = 7, 2H, 5-Et CH_2), 4.34 (q, J = 7, 2H, O-Et CH_2), 8.50 (s, 1H, H-3)
IIc	1717, 1608, 1482, 1420, 1380	0.99 (t, J = 7, 3H, Pr CH_3), 1.35 (t, J = 7, 3H, Et CH_3), 1.72 (sex, J = 7, 2H, Pr CH_2), 3.09 (t, J = 7, 2H, Pr CH_2), 4.33 (q, J = 7, 2H, Et CH_2), 8.49 (s, 1H, H-3)
IId	1715, 1603, 1482, 1418, 1377	1.35 [d, J = 7, 6H, $(CH_3)_2C$], 1.36 (t, J = 6.5, 3H, CH_3), 3.85 (h, J = 7, 1H, $CHMe_2$), 4.34 (q, J = 7, 2H, CH_2), 8.48 (s, 1H, H-3)
IIe	1723, 1588, 1488, 1410, 1372	1.36 (t, J = 7, 3H, CH_3), 1.49 [s, 9H, $(CH_3)_3C$], 4.32 (q, J = 7, 2H, CH_2), 8.52 (s, 1H, H-3)
IIf	1723, 1613, 1483, 1442, 1378	3.82 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 7.29 (s, 5H, C_6H_5), 8.48 (s, 1H, H-3)
IIg	1720, 1612, 1592, 1570, 1465, 1447, 1413, 1375	1.32 (t, J = 7, 3H, CH_3), 4.32 (q, J = 7, 2H, CH_2), 7.51 (m, 3H, 2H ar *m* + 1H ar *p*), 8.10 (m, 2H, 2H ar *o*), 8.65 (s, 1H, H-3) [a]
IIh	1726, 1615, 1480, 1443, 1382	3.49 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O_2C), 4.89 (s, 2H, CH_2), 8.58 (s, 1H, H-3)
IIi	1727, 1614, 1485, 1441, 1382	2.81 (t, J = 7, 2H, CH_2), 3.46 (t, J = 7, 2H, CH_2), 3.71 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 8.51 (s, 1H, H-3)
III	1725, 1613, 1484, 1422, 1382	1.24 (t, J = 6.5, 3H, Et CH_3), 1.36 (t, J = 6.5, 3H, Et CH_3), 1.8-2.6 (m, 4H, 2 CH_2), 3.20 (t, J = 7, 2H, CH_2CO), 4.13 (q, J = 6.5, 2H, CH_2O), 4.34 (q, J = 6.5, 2H, CH_2O), 8.52 (s, 1H, H-3) [b]
IIm	1745, 1611, 1468, 1414, 1378	1.36 (t, J = 7, 3H, CH_3), 1.42 (t, J = 7, 3H, CH_3), 4.38 (q, J = 7, 2H, CH_2), 4.50 (q, J = 7, 2H, CH_2), 8.64 (s, 1H, H-3)

[a] Reference [17] (deuteriochloroform): δ 1.35 (t, J = 7.2, CH_3), 4.37 (q, J = 7.2, CH_2), 7.25-8.39 (m, C_6H_5), 8.66 (s, H-3). [b] In DMSO-d_6.

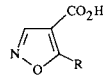
Esters **IIa-l** were converted, generally in satisfactory yields, to the corresponding 4-isoxazolecarboxylic acids **IIIa-h,n,o** (Tables III, IV) by reflux with mixtures of hydrochloric and acetic acids or with concentrated hydrochloric acid alone.

The hydrolysis of ester **IIm** gave no result, whereas **V** did not afford the corresponding acid, but lactone **VI**, whose structure was unequivocally proved by the ir absorptions typical of γ-lactone carbonyl and hydroxy groups, as well as by ^{1}H nmr singlet for hydroxy group (see Experimental).

Attempted thermic decarboxylation of some acids **III** gave no results, since complex mixtures of products were obtained, whose separation proved to be difficult. This is not surprising, since it is known that isoxazole carboxylic acids are usually decomposed on heating above their melt-

Table III

5- Substituted 4-Isoxazolecarboxylic Acids **IIIa-h,n,o**



Formula Number	R	Ratio v/v conc.HCl-AcOH	Reflux Time (hours)	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./ Found C	H	N
IIIa	CH_3	1:1	1	55	147-149 [a] [b]	$C_5H_5NO_3$	47.25 47.27	3.96 3.97	11.02 11.10
IIIb	CH_2CH_3	3:1	3	95	85-87 [c]	$C_6H_7NO_3$	51.06 51.31	5.00 5.03	9.92 10.01
IIIc	$(CH_2)_2CH_3$	3:1	2	82	91-92 [c]	$C_7H_9NO_3$	54.19 54.44	5.85 5.87	9.03 9.07
IIId	$CH(CH_3)_2$	1:1	3	76	80-81 [c]	$C_7H_9NO_3$	54.19 53.98	5.85 5.81	9.03 8.99
IIIe	$C(CH_3)_3$	1:2	12	80	135-136 [c]	$C_8H_{11}NO_3$	56.80 56.91	6.55 6.55	8.28 8.36
IIIf	$CH_2C_6H_5$	1:2	8	74	150-151 [a]	$C_{11}H_9NO_3$	65.02 64.87	4.46 4.44	6.89 7.00
IIIg	C_6H_5	1:2	7	78	154-155 [a] [d]	$C_{10}H_7NO_3$	63.49 63.49	3.73 3.70	7.40 7.40
IIIh	CH_2OCH_3	conc. HCl	0.5	71	69-70 [a]	$C_6H_7NO_4$	45.86 45.74	4.49 4.45	8.91 8.61
IIIn	$(CH_2)_2CO_2H$	1:2	4	70	189-191 [e]	$C_7H_7NO_5$	45.41 45.29	3.81 3.81	7.57 7.49
IIIo	$(CH_2)_3CO_2H$	conc. HCl	2.5	54	143-144 [f]	$C_8H_9NO_5$	48.25 48.37	4.55 4.55	7.03 7.14

[a] From petroleum ether (bp 40-70°) - diethyl ether 2:1. [b] Reference [7], mp 143-144°; reference [10], mp 146-147°. [c] From petroleum ether. [d] Reference [9], mp 155-156°. [e] From ethyl acetate. [f] From diethyl ether- ethyl acetate 2:1.

Table IV

IR and ^1H NMR Spectral Data of Compounds **IIIa-h,n,o**

Compound	IR, cm^{-1}	^1H NMR, δ
IIIa	3200-2500, 1696, 1615, 1490, 1462	2.71 (s, 3H, CH_3), 8.52 (s, 1H, H-3), 12.07 (s, 1H, CO_2H; disappears with deuterium oxide)
IIIb	3100-2500, 1695, 1608, 1486, 1460	1.35 (t, J = 8, 3H, CH_3), 3.19 (q, J = 8, 2H, CH_2), 8.58 (s, 1H, H-3), 12.24 (s, 1H, CO_2H; disappears with deuterium oxide)
IIIc	3100-2500, 1695, 1608, 1485, 1460	1.03 (t, J = 7, 3H, CH_3), 1.78 (sex, J = 7, 2H, CH_2), 3.16 (t, J = 7, 2H, CH_2), 8.62 (s, 1H, H-3), 12.42 (s, 1H, CO_2H; disappears with deuterium oxide)
IIId	3100-2500, 1694, 1604, 1486, 1467	1.39 [d, J = 7, 6H, $(CH_3)_2C$], 3.89 (mc, 1H, $CHMe_2$), 8.57 (s, 1H, H-3), 12.00 (s, 1H, CO_2H; disappears with deuterium oxide)
IIIe	3200-2500, 1702, 1586, 1492, 1472	1.52 [s, 9H, $(CH_3)_3C$], 8.62 (s, 1H, H-3), 12.36 (s, 1H, CO_2H; disappears with deuterium oxide)
IIIf	3200-2500, 1695, 1612, 1485, 1455	4.50 (s, 2H, CH_2), 7.35 (s, 5H, C_6H_5), 8.58 (s, 1H, H-3), 11.41 (s, 1H, CO_2H; disappears with deuterium oxide)
IIIg	3000-2500, 1693, 1610, 1592, 1571, 1470, 1448	7.60 (mc, 3H, 2H ar *m* + 1H ar *p*), 8.10 (mc, 2H, 2H ar *o*), 8.72 (s, 1H, H-3), 10.92 (br s, 1H, CO_2H; disappears with deuterium oxide)
IIIh	3200-2500, 1702, 1613, 1448	3.54 (s, 3H, CH_3O), 4.95 (s, 2H, CH_2), 8.66 (s, 1H, H-3), 11.70 (s, 1H, CO_2H; disappears with deuterium oxide)
IIIn	3200-2500, 1693, 1602, 1470, 1442 [a]	2.71 (t, J = 7, 2H, CH_2), 3.33 (t, J = 7, 2H, CH_2CO), 8.78 (s, 1H, H-3), ~12 (br s, 2H, $2CO_2H$; disappears with deuterium oxide) [b]
IIIo	3300-2500, 1690, 1600, 1466, 1442 [a]	1.7-2.5 (m, 4H, 2 CH_2), 3.14 (t, J = 7, 2H, CH_2CO), 8.79 (s, 1H, H-3), ~12.5 (br s, 2H, 2 CO_2H; disappears with deuterium oxide) [b]

[a] In potassium bromide. [b] In DMSO-d_6.

ing points without giving the corresponding isoxazoles [11].

Ethyl or methyl esters **IIa-h,m** gave as 3-unsubstituted isoxazoles the well known isomerization to the corresponding ethyl or methyl α-cyano-β-oxoalkanoates **VIIa-h,m** (Table V), generally in high yields, by treatment with cold sodium ethoxide or methoxide, respectively.

Table V

Esters of 2-Cyano-3-oxoalkanoic Acids **VIIa-h,m-o**

$R-CO-CH(CN)-CO_2R' \rightleftharpoons R-C(OH)=C(CN)-CO_2R'$

Formula Number	R	R'	Yield %	Bp °C / mm or mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
VIIa	CH_3	C_2H_5	97	110-115 / 20 [a]	$C_7H_9NO_3$	54.19 53.99	5.85 5.80	9.03 9.26
VIIb	CH_2CH_3	C_2H_5	93	115-120 / 20 [b]	$C_8H_{11}NO_3$	56.80 56.72	6.55 6.56	8.28 8.50
VIIc	$(CH_2)_2CH_3$	C_2H_5	87	125-130 / 20 [c]	$C_9H_{13}NO_3$	59.00 59.09	7.15 7.24	7.64 7.98
VIId	$CH(CH_3)_2$	C_2H_5	96	115-120 / 20 [d]	$C_9H_{13}NO_3$	59.00 59.25	7.15 7.29	7.64 7.81
VIIe	$C(CH_3)_3$	C_2H_5	92	120-125 / 20	$C_{10}H_{15}NO_3$	60.90 60.84	7.66 7.72	7.10 7.12
VIIf	$CH_2C_6H_5$	CH_3	50	51-52 [e]	$C_{12}H_{11}NO_3$	66.35 66.47	5.10 5.06	6.45 6.55
VIIg	C_6H_5	C_2H_5	51	35-36 [f] [g]	$C_{12}H_{11}NO_3$	66.35 66.53	5.10 5.12	6.45 6.61
VIIh	CH_2OCH_3	CH_3	78	72-73 [h]	$C_7H_9NO_4$	49.12 49.26	5.30 5.39	8.18 8.28
VIIm	$CO_2C_2H_5$	C_2H_5	48	92-93 [i]	$C_9H_{11}NO_5$	50.70 50.51	5.20 5.16	6.57 6.61
VIIn	$(CH_2)_2CO_2H$	CH_3	65	134-135 [i]	$C_8H_9NO_5$	48.25 48.44	4.55 4.54	7.03 7.15
VIIo	$(CH_2)_3CO_2H$	C_2H_5	77	134-135 [i] [l]	$C_{10}H_{13}NO_5$	52.86 53.10	5.77 5.81	6.16 6.33

[a] Reference [7], bp 106-107° / 15; 68% yield; reference [13], bp 106-111° / 20; 57% yield; reference [14], bp 88-89° / 6. [b] Reference [15], bp 155-165° / 50. [c] Reference [15], bp 166-178° / 66. [d] Reference [15], bp 170-177° / 85. [e] From petroleum ether - diethyl ether 1:1. [f] From petroleum ether - diethyl ether 2: 1. [g] References [9] and [16], mp 40-41°. [h] From petroleum ether. [i] From anhydrous diethyl ether. [l] Reference [12], mp 134°.

Diester **III** afforded in high yield nitrile **VIIo**, where the ester group initially in the 5-side chain was surprisingly hydrolyzed. The structure of **VIIo** was unequivocally proved not only by comparison with the product previ-

ously synthesized from glutaric anhydride and ethyl sodium cyanoacetate [12], but also by comparison of the ^1H nmr spectral data of **III** and **VIIo**, showing in the latter the disappearance of the less deshielded ethoxy group present in **III** (see Tables II, VI).

Table VI

IR and ^1H NMR Spectral Data of Compounds **VIIa-h,m-o**

Compound	IR, cm^{-1}	^1H NMR, δ
VIIa	2228, 1658, 1602	1.37 (t, J = 7, 3H, Et CH_3), 2.36 (s, 3H, CH_3), 4.36 (q, J = 7, 2H, CH_2), 13.65 (br s, 1H, OH; disappears with deuterium oxide) [a]
VIIb	2225, 1658, 1592	1.24 (t, J = 7, 3H, CH_3), 1.36 (t, J = 7, 3H, CH_3), 2.64 (q, J = 7, 2H, CH_2), 4.33 (q, J = 7, 2H, CH_2O), 13.55 (br s, 1H, OH; disappears with deuterium oxide)
VIIc	2228, 1657, 1593	1.02 (t, J = 7, 3H, Pr CH_3), 1.35 (t, J = 7, 3H, Et CH_3), 1.4-2.2 (m, 2H, Pr CH_2), 2.60 (t, J = 7, 2H, Pr CH_2), 4.33 (q, J = 7, 2H, CH_2O), 13.72 (s, 1H, OH; disappears with deuterium oxide)
VIId	2225, 1656, 1587	1.25 [d, J = 7, 6H, $(CH_3)_2C$], 1.37 (t, J = 7, 3H, CH_3), 3.16 (h, J = 7, 1H, $CHMe_2$), 4.35 (q, J = 7, 2H, CH_2O), 13.82 (br s, 1H, OH; disappears with deuterium oxide)
VIIe	2225, 1652, 1573	1.34 (t, J = 7, 3H, CH_3), 1.36 [s, 9H, $(CH_3)_3C$], 4.34 (t, J = 7, 2H, CH_2O), 14.59 (br s, 1H, OH; disappears with deuterium oxide)
VIIf	2230, 1660, 1595	3.88 (s, 5H, CH_3 and CH_2), 7.37 (s, 5H, C_6H_5), 13.55 (br s, 1H, OH; disappears with deuterium oxide)
VIIg	2225, 1660, 1597, 1565	1.39 (t, J = 7, 3H, CH_3), 4.40 (q, J = 7, 2H, CH_2), 7.55 (m, 3H, 2H ar *m* + 1H ar *p*), 8.03 (m, 2H, 2H ar *o*), 14.24 (s, 1H, OH; disappears with deuterium oxide)
VIIh	2223, 1662, 1597	3.50 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 4.37 (s, 2H, CH_2), ~13.5 (very br s, 1H, OH; disappears with deuterium oxide)
VIIm	2232, 1747, 1673, 1600	1.39 (t, J = 7, 6H, 2 CH_3), 4.44 (q, J = 7, 4H, 2 CH_2), ~11 (very br s, 1H, OH; disappears with deuterium oxide)
VIIn	2900-2500, 2228, 1735, 1658, 1595	2.6-3.2 (m, 4H, 2 CH_2), 3.90 (s, 3H, CH_3), ~8.0 (very br s, 1H, CO_2H; disappears with deuterium oxide), ~13.2 (very br s, 1H, OH; disappears with deuterium oxide)
VIIo	2900-2500, 2228, 1712 1660, 1597	1.35 (t, J = 7, 3H, Et CH_3), 1.7-3.0 (m, 6H, 3 CH_2), 4.34 (q, J = 7, 2H, Et CH_2), ~10.5 (very br s, 2H, OH + CO_2H; disappears with deuterium oxide)

[a] Reference [14] : δ 1.38 (Et CH_3), 2.37 (CH_3), 4.38 (Et CH_2), 13.45 (OH).

Similarly, diester **IIi** gave nitrile **VIIn**, whose structure resulted by comparison of ^1H nmr spectra of **IIi** e **VIIn**, showing in the latter the disappearance of the less deshielded methoxy group present in **IIi**.

The above α-ketonitriles are in the tautomeric form, as it was shown by their ir nitrile absorptions at 2223-2232 cm^{-1} and ^1H nmr broad singlets at δ 13.5-14.6 for the hydroxy group (Table VI).

Nitriles **VIIa,g** are already known and were prepared by the above procedure [7,9]; nitrile **VIIa** was also prepared by reaction of ketene with ethyl cyanoacetate [13,14], whereas **VIIb,c,d** were obtained more than a century ago by reaction of ethyl sodium cyanoacetate with the corresponding acyl chloride [15].

In conclusion, the reaction of esters of 2-dimethylaminomethylene-3-oxoalkanoic acids with hydroxylamine seems to offer another useful synthetic pathway to 5-substituted 4-isoxazolecarboxylic acids, and work is in progress to synthesize some of their derivatives which could be of pharmacological interest.

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 Esters of 5-Substituted 4-Isoxazolecarboxylic Acids **IIa-m**.

A solution of **Ia-m** [2,5] (10 mmoles) and hydroxylamine hydrochloride (0.695 g, 10 mmoles) in methanol (10 ml) was refluxed for 1 hour. The reaction mixture was cooled, diluted with water (10 ml) and extracted thoroughly with diethyl ether. The extracts were dried (magnesium sulfate) and evaporated under reduced pressure to give a residue which was chromatographed on Florisil, using petroleum ether (bp 40-70°) as eluant. The compounds were further purified by bulb-to-bulb distillation *in vacuo* or by recrystallization from petroleum ether (**IIe**). Ester **IIa** contained a little amount of the isomer 3-methyl ester, as evidenced by a ^1H nmr singlet at δ 2.50. A ratio of about 96/4 of **IIa** with respect to the isomer was calculated on the basis of 5-methyl and 3-methyl group singlets at δ 2.70 and 2.50, respectively. The isomer 3-methyl ester could not be removed either by repeated distillations *in vacuo* or column chromatographies on silica gel.

Elemental analyses, yields and mp or bp of these esters are reported in Table I; ir and ^1H nmr spectral data in Table II.

Methyl 4-(2,2-Dimethyl-1-oxopropyl)-5-isoxazolecarboxylate **V**.

This ester was obtained in 33% yield starting from **IV** [5] and following the above general procedure, colorless liquid, bp 90-95°/0.5; ir (chloroform): ν max 1740, 1692, 1556, 1490, 1467, 1438, 1370 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 [s, 9H, $(CH_3)_3C$], 3.98 (s, 3H, CH_3O), 8.94 (s, 1H, H-3).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.31; N, 6.91.

General Procedure for 5-Substituted 4-Isoxazolecarboxylic Acids **IIIa-h,n,o**.

A solution of ester **II** (10-30 mmoles) in the appropriate concentrated hydrochloric-acetic acids mixture or concentrated hydrochloric acid alone (Table II) (30 ml) was refluxed for a certain time. After cooling, the solution was diluted with water (30 ml), made alkaline (*p*H ~7.5) with sodium carbonate and extracted with diethyl ether. The cold aqueous solution was acidified with 6*N* hydrochloric acid (*p*H ~1) and extracted thoroughly with diethyl ether (chloroform in the case of **IIl**). The extracts were washed once with water, dried (magnesium sulfate) and evaporated under reduced pressure to give a solid residue which was recrystallized from a suitable solvent.

Acid **IIIa** could be obtained free from 3-methyl isomer by the following procedure.

The precipitate obtained after acidification was filtered, dissolved in diethyl ether, the solution was washed once with water and worked up as above. The first acid aqueous solution contained indeed practically all the 3-methyl acid, more soluble than the 5-methyl isomer **IIIa**. From this solution a mixture of the two isomers, enriched in 3-methyl acid, can be obtained by diethyl ether extraction.

Elemental analyses, hydrolysis mixtures, reflux times, yields

and mp of these acids are reported in Table III; ir and ^{1}H nmr spectral data in Table IV.

4-*t*-Butyl-4-hydroxyfuro[3,4-*d*]isoxazol-6(4*H*)-one **VI**.

This lactone was obtained in 65% yield by refluxing for 1 hour a solution of ester **V** in concentrated hydrochloric acid-acetic acid 1:2; mp 72-74° from petroleum ether-diethyl ether 1:1; ir (chloroform): ν max 3370, 2900-2400, 1783, 1730, 1690, 1555, 1488, 1465 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.49 [s, 9H, $(CH_3)_3C$], 9.23 [s, 1H, OH, disappears with deuterium oxide), 9.36 (s, 1H, H-3).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.88; H, 5.62; N, 7.17.

General Procedure for Esters of 2-Cyano-3-oxoalkanoic Acids **VIIa-h,m-o**.

A cold solution of sodium ethoxide (in the case of **IIa-e,g,l,m**) or methoxide (in the case of **IIf,h,i**) in ethanol or methanol, prepared from sodium (0.35 g, 15.2 mmoles) and anhydrous ethanol or methanol (10 ml), respectively, was slowly added with stirring to an ice-cooled solution of **II** (10 mmoles) in anhydrous diethyl ether (100 ml). The reaction mixture was stirred at room temperature for 12 hours, evaporated under reduced pressure and the residue was diluted with cold water (10 ml). The ice-cooled solution was acidified with 6*N* hydrochloric acid (*p*H ~1) and the precipitate was extracted thoroughly with diethyl ether (**VIIa-h**) or chloroform (**VIIn-o**). The extracts were dried (magnesium sulfate) and evaporated under reduced pressure to give a residue which was recrystallized from a suitable solvent or purified by bulb-to-bulb distillation *in vacuo*.

Nitrile **VIIn** contained a little amount of diester **VII** (R = $CH_2CH_2CO_2CH_3$, R' = CH_3). Therefore it was dissolved in chloroform and the solution was extracted three times with a saturated aqueous solution of sodium hydrogen carbonate. The ice-cooled solution was acidified and worked up as above.

Elemental analyses, yields and bp or mp of these nitriles are reported in Table V; ir and ^{1}H nmr spectral data in Table VI.

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REFERENCES AND NOTES

[1] Part of the 'Dottorato di Ricerca' thesis of P. Fossa.

[2] G. Menozzi, L. Mosti and P. Schenone, *J. Heterocyclic Chem.*, **24**, 1669 (1987).

[3] L. Mosti, G. Menozzi, P. Schenone, P. Dorigo, R. M. Gaion, F. Benetollo and G. Bombieri, *Eur. J. Med. Chem.*, **24**, 517 (1989).

[4] P. Schenone, L. Sansebastiano and L. Mosti, *J. Heterocyclic Chem.*, **27**, 295 (1990).

[5] G. Menozzi, L. Mosti, P. Schenone, D. Donnoli, F. Schiariti and E. Marmo, *Farmaco*, **45**, 167 (1990).

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

[7] H. Yasuda, *Yakugaku Zasshi*, **79**, 836 (1959); *Chem. Abstr.*, **54**, 1493 e (1960).

[8] G. Doleschall and P. Seres, *J. Chem. Soc., Perkin Trans. 1*, 1875 (1988). In this paper ester **IIa** was erroneously described as the acid **IIIa**.

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

[10] N. K. Kochetkov, E. D. Khomutova and M. V. Bazilevskii, *Zh. Obshch. Khim.*, **28**, 2736 (1958); *Chem. Abstr.*, **53**, 9187 i (1959).

[11] A. Quilico, in Five- and Six-Membered Compounds with Nitrogen and Oxygen, R. H. Wiley ed, Interscience, NY, 1962, p 82-88.

[12] F. Sorm, J. Gut and P. Kankowsky, *Collect. Czech. Chem. Commun.*, **15**, 99 (1950); *Chem. Abstr.*, **44**, 8329h (1950).

[13] T. Isoshima, *Nippon Kagaku Zasshi*, **77**, 425 (1956); *Chem. Abstr.*, **52**, 8948f (1958).

[14] J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2105 (1964).

[15] A. Haller, *Compt. Rend. Acad. Sci. Paris*, **106**, 1083 (1888).

[16] A. Haller, *Compt. Rend. Acad. Sci. Paris*, **105**, 169 (1887).

[17] R. Huisgen and M. Christl, *Chem. Ber.*, **106**, 3291 (1973).