2-Methylisoxazolin-5-ones III.
Carboxylic Acids and their Derivatives (I)

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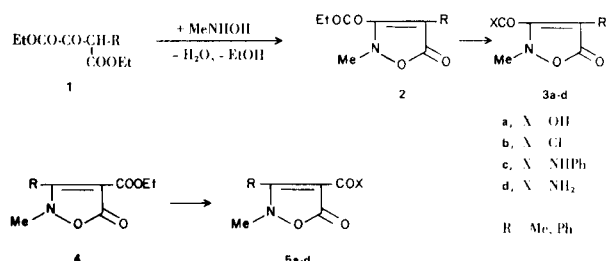
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Carbethoxy-substituted 2-methylisoxazolin-5-ones and several functional derivatives have been
prepared. Spectral properties of the corresponding carboxylic acids are discussed. These acids
are stronger when the carboxy group is in position 3 than when in position 4 of the heterocycle.

The direct synthesis of N-methylisoxazolin-5-one deriv-
atives from β-oxoesters and N-methylhydroxylamine (2)
has been successfully extended to the preparation of sub-
stituted 3-carbethoxy-N-methylisoxazolin-5-one. Substi-
tuted diethyl oxalacetates (1, R = Me or Ph) were the
starting materials for the synthesis of esters 2 (R = Me or
Ph).

Esters 4 are known, with R = H (3,4), R = Me (4), and
R = Ph (5): only the compound 4 (R = Me) has been
obtained directly from the appropriate β-oxoester (i.e.,
diethyl acetylmalonate), the others having been prepared
respectively from diethyl ethoxymethylenemalonate and
N-methylhydroxylamine (4, R = H) and by methylating
the corresponding isoxazolin-5-one derivative (4, R = Ph).
We have obtained the last compound directly from diethyl
(α-methoxybenzylidene)malonate and N-methylhydroxyl-
amine.

Hydrolysis of the esters 2 and 4 to the corresponding
acids 3a and 5a, respectively, can be accomplished by
treatment with aqueous alkali followed by acidification:
care must be taken in the case of esters 2, as acids 3a
decompose easily in alkaline solutions. The ester 4 (R = H)
undergoes ring-opening with bases, as known (4). Esters

2 are easily hydrolysed by concentrated hydrochloric acid
as well, whereas esters 4 are not. This different behaviour
is probably related to the different strength of acids 3a
and 4a (s. Table I).

All acids prepared can be converted into chlorides (3b
and 5b) and these in anilides (3c and 5c) or amides (3d
and 5d). Amides 3d can be obtained directly from esters
2 and aqueous ammonia. All acids 3a and 5a (R = Me or
Ph) decompose on heating. Decomposition has been
limited to decarboxylation only for the acid 5a (R = Ph),
which gave the known (2) 2-methyl-3-phenylisoxazolin-
5-one. A few examples of decarboxylation at isoxazole
position 4 are known (6), while decarboxylation of 3-
carboxy derivatives is a more common process, which,
however, is always accompanied by ring-opening (7,8).

Acids 3a (R = Me or Ph) are stronger than their isomers
5a (R = Me or Ph) (Table I). This difference can be
ascribed in part to the higher electron density at position
4 than at position 3, already noticed in connection with
bromination of some isoxazolin-5-ones by N-bromosuc-
cinimide (2), and in part to intramolecular H-bonding,
which is possible only in acids 5a. In addition, a more
marked dependence of K_a on concentration is observed
for acids 3a than for acids 5a. This is related to hydrogen
bonding, intermolecular (acids 3a) or intramolecular (acids
5a).

All acids 3a and 5a (R = Me or Ph) show in their
spectra (solid phase) broad structured bands around 2600
cm^{-1}, indicating association via hydrogen bonds. In solid
phase, intermolecular association occurs between carboxyl
groups, as demonstrated by the changes in ν (C=O) fre-
quencies. The carboxyl ν (C=O) bands (1660-1695 cm^{-1},
solid phase, Table I) are shifted in solution to higher

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Table I

Properties of Acids 3a and 5a and Esters 2 and 4

Ir (b)

Compounds	pK_a (a)	ν (C=O) (ring) Solid (c)	ν (C=O) (ring) Solution (d)	ν (C=O) (carboxyl) Solid (c)	ν (C=O) (carboxyl) Solution (d)
3a, R = Me	3.15	1740	1735	1690	1735
3a, R = Ph	3.0	1725	1735	1695	1735
5a, R = Me	4.5	{ 1790 1750	1740	1675	1720
5a, R = Ph	4.1	1775 (e)	1745	1660 (e)	1715
2, R = Me		1755	1750, sh (f)	1735	1730 (f)
2, R = Ph		1725	1730	1720, sh	1730
4, R = Me		1745	1745	1690	1690
4, R = Ph		{ 1760 1740, sh	1760	1690	1695

(a) In water, at 25°; concentration ca. 10^{-3} M. (b) Maximum frequencies in the ν (C=O) region (cm^{-1}); sh = shoulder. (c) Nujol mulls. (d) Solvent, chloroform. (e) Reported (11) 1780 (ring), 1656 (carboxyl). (f) In dioxane solution, the 1730 and 1750 cm^{-1} bands are well resolved.

Table II

Uv Spectra of 2-Methylisoxazolin-5-one Acids and Esters (a)

Acids	Water	Solvents Dilute Perchloric acid	Solvents 70% Perchloric acid	Ethanol		Esters	Methanol	Solvents 70% Perchloric acid	
3a, R = Me	281 (3.87)	307 (3.81)(b)	294 (3.80)	298	(3.82)	2, R = Me	209 (3.78) 305 (3.78)	200 291	(3.73) (3.87)
3a, R = Ph	244 (3.85) 294 (3.96)	200 (4.17)(c) 237 (3.74) 316 (3.84)	202 (4.15) 224 (3.84) 306 (3.73)	205 241 302	(4.05) (3.82) (3.92)	2, R = Ph	234 (3.80) 318 (3.90)	221, sh (3.85) 302	(3.72)
5a, R = Me	225 (3.89) 262 (4.08)	228 (3.89)(b) 258 (4.07)	229 (3.91) 248 (3.89)	221 268	(3.89) (4.13)	4, R = Me	223 (3.95) 265 (4.15)	231 240, sh	(3.98) (3.95)
5a, R = Ph	202 (4.16) 221 (4.03) 275 (3.96)	203 (4.11)(b) 227 (3.97) 272 (3.98)	202 (4.09) 227 (3.94) 262 (4.09)	206 220, sh 280	(4.24) (4.12) (4.05)	4, R = Ph	203 (4.25) 220 (4.15) 276 (4.09)	221 259	(3.80) (3.90)

(a) λ Max in nm (log ε), region 200 to 350 nm. (b) About 5.8M in perchloric acid. (c) About 2.3M in perchloric acid. An isosbestic point at 310 nm (log ε = 3.83) is exhibited in aqueous solutions 0 to 2.3M in perchloric acid.

frequencies (1715-1735 cm^{-1}, chloroform) due to breaking of the intermolecular hydrogen bonds. However, on the contrary, nuclear ν (C=O) bands are scarcely affected by phase change in acids 3a (where intramolecular hydrogen bonding is impossible), and in acids 5a are shifted in solution to lower frequencies, owing to occurrence of intramolecular hydrogen bonds. No significant difference, in the ν (C=O) region, is observed between the spectra of esters in solution and in the solid phase.

In the discussion of uv spectra (Table II), it must be considered that in dilute aqueous solutions, acids 3a are completely and acids 5a are in part dissociated. The spectra in 0.1M aqueous sodium hydroxide (which are not reported in Table II, because they change with time), registered immediately after dissolution, are close to the corresponding spectra in water.

In the spectra of acids 5a (R = Me or Ph), the absorption with λ max near 220 nm is ascribed to the system

C=C(CO)-COOH, cf., 2-methyl-4-carbethoxyisoxazolin-5-one [methanol, 223 (3.98), 270 (4.14)] and diethyl ethyl-idenemalonate [225 (3.75), no solvent given] (9); this band is unaffected in 70% perchloric acid, the apparent red-shift being due to the closeness of the other band. The maximum at 262 nm of acid 5a (R = Me) refers to the conjugated ring system, as a similar band is found in 2-methylisoxazolin-5-one (10). As expected, this is blue-shifted and considerably reduced in intensity with 70% perchloric acid as solvent. The band at 275 nm of acid 5a (R = Ph) undergoes blue-shift and a slight intensity *enhancement* in 70% perchloric acid. The same feature is observed in 2-methyl-3-phenylisoxazolin-5-one [methanol, 206 (4.21), 248 (4.05), 277 (3.96); 70% perchloric acid, 202 (4.12), 258 (4.21)] and is ascribed to steric relief to the conjugation between the rings, due to protonation at the nitrogen atom. No such intensity increase is found in the corresponding ester (4, R = Ph), owing to 4-substitution, but appears again in the acid, where carboxyl and carbonyl are linked by hydrogen bonding.

The spectra of acids 3a (R = Me or Ph) in diluted acid medium resemble those of the corresponding esters (2, R = Me or Ph) in methanol, thus ionic structures are ruled out. The broad absorption of acid 3a (R = Me) with maximum at 307 nm (dilute perchloric acid, shoulder around 270 nm) includes in fact the band found for 2,4-dimethylisoxazolin-5-one [methanol, 272 (3.96)] and a lower frequency absorption arising from a conjugated system in which both the carboxyl group and the nitrogen lone pair are involved, since a blue-shift is observed in 70% perchloric acid, as well as in water (or 0.1*M* aqueous sodium hydroxide). A similar situation is encountered with acid 3a (R = Ph), compared to 2-methyl-4-phenyl-isoxazolin-5-one [methanol, 205 (4.07), 218 (3.98), 248 (4.00), 284 (4.01), 301 (4.06)].

EXPERIMENTAL

Acid dissociation constants were measured potentiometrically with a Metrohm Potentiograph model E 336.

Spectra were registered on Perkin-Elmer spectrometers model 337 (ir), model 124 (uv), and model R 32 (nmr).

2,4-Dimethyl-3-carboxyisoxazolin-5-one (3a, R = Me) and its Derivatives.

The ester 2 (R = Me) was obtained in 90% yield by refluxing for 6 hours a pyridine solution of ethyl α-oxalpropionate and *N*-methylhydroxylamine hydrochloride (10% excess). Removal of the solvent and mixing with cold water afforded the product, m.p. 33-34° (from petroleum ether); nmr (deuteriochloroform): 1.4 (t, 3H), 2.06 (s, 3H), 3.41 (s, 3H, N-CH₃), 4.45 δ (q, 2H).

Anal. Calcd. for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.85; H, 6.02; N, 7.87.

Hydrolysis, carried out by gently refluxing the ester in concentrated hydrochloric acid, or by a 3 hour treatment of the ester in 10% cold aqueous sodium hydroxide followed by acidification,

gave the acid (3a, R = Me), m.p. 159-161° dec. (from water), yield 70 or 75%, respectively.

Anal. Calcd. for $C_6H_7NO_4$: C, 45.87; H, 4.49; N, 8.91. Found: C, 45.80; H, 4.43; N, 8.83.

The acyl chloride 3b (R = Me) was prepared by refluxing the acid in thionyl chloride, b.p. 96-98° at 0.8 torr, or 70-72° at 0.2 torr (the product solidified on cooling).

Anal. Calcd. for $C_6H_6ClNO_3$: Cl, 20.19; N, 7.98. Found: Cl, 20.05; N, 8.02.

By treatment of the chloride with ammonia in ether, or of the ester with concentrated aqueous ammonium hydroxide, the amide (3d, R = Me) was obtained, m.p. 149-150° dec. (from 1:1 di-oxane-benzine), soluble in water.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.43; H, 5.22; N, 17.80.

The anilide (3c, R = Me) was prepared from the chloride and aniline in benzene, m.p. 102-104° (from 50% ethanol).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.88; H, 5.32; N, 12.03.

2,4-Dimethylisoxazolin-5-one 3-carboxy(*N*,*N*-diethyl)amide was obtained from the chloride and diethylamine in ether, b.p. 123-125° at 0.05 torr, soluble in water.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.55; H, 7.69; N, 13.20.

2-Methyl-3-carboxy-4-phenylisoxazolin-5-one (3a, R = Ph) and its Derivatives.

A mixture of *N*-methylhydroxylamine hydrochloride (excess) and diethyl oxalphenylacetate sodium salt was refluxed 8 hours in anhydrous ethanol. Filtration, concentration, and admixture with water gave 81% of the crude ester (2, R = Ph), m.p. 77-78° (from light petroleum 60-80); nmr (deuteriochloroform): 1.2 (t, 3H), 3.5 (s, 3H), 4.3 (q, 2H), 7.4 δ (m, 5H).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.46; H, 5.14; N, 5.75.

The acid (3a, R = Ph) was prepared by either acid (yield 60%) or alkaline (yield 50%) hydrolysis, as described above, m.p. 159-160° dec. (from water).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N, 6.39. Found: C, 60.01; H, 3.99; N, 6.12.

The acyl chloride (3b, R = Ph), prepared as the methyl derivative (3b, R = Me), had b.p. 170° at 0.7 torr, m.p. 41-42°.

Anal. Calcd. for $C_{11}H_8ClNO_3$: C, 55.59; H, 3.40; Cl, 14.91; N, 5.89. Found: C, 55.30; H, 3.40; Cl, 16.00; N, 5.90.

The amide (3d, R = Ph) was obtained from the chloride or from the ester, m.p. 194-195° dec. (from water).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.50; H, 4.71; N, 12.74.

The anilide (3c, R = Ph) had m.p. 178-179° (from ethanol), yield 92%.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.14; H, 4.91; N, 9.52.

2,3-Dimethyl-4-carboxyisoxazolin-5-one (5a, R = Me) and its Derivatives.

The preparation of the ester (4, R = Me) has been previously described (4), but a better yield was obtained in pyridine (72%); nmr (deuteriochloroform): 1.32 (t, 3H), 2.51 (s, 3H), 3.61 (s, 3H, N-CH₃), 4.25 δ (q, 2H).

The acid (5a, R = Me) was prepared according to the literature, 78% yield, m.p. 229-230° dec. [lit. (4), 242-243° dec.].

A suspension of the acid in phosphorus trichloride was treated with phosphorus pentachloride; after heating 1 hour at 90°, the

solvent was removed and the residue washed with light petroleum and dissolved in chloroform. The acyl chloride (5b, R = Me) precipitated by admixture of the chloroform solution with benzene, m.p. 116-118°.

Anal. Calcd. for $C_6H_6ClNO_3$: C, 41.05; H, 3.44; Cl, 20.19; N, 7.98. Found: C, 41.15; H, 3.55; Cl, 18.80; N, 7.89.

The anilide (5c, R = Me) was prepared in chloroform by addition of the chloride to a mixture of aniline and pyridine. After removal of the solvent, the residue was washed with water and recrystallized from anhydrous ethanol, m.p. 172-174°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.09; H, 5.27; N, 12.24.

Diethyl (α-Methoxybenzylidene)malonate.

This was prepared from diethyl benzoylmalonate and diazomethane in ether, b.p. 140° at 0.03 torr; nmr (carbon tetrachloride): 0.94 (t, 3H), 1.28 (t, 3H), 3.47 (s, 3H), 3.89 (q, 2H), 4.22 (q, 2H), 7.25-7.60 δ (m, 5H).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.52; H, 6.37.

2-Methyl-3-phenyl-4-carboxyisoxazolin-5-one (5a, R = Ph) and its Derivatives.

A pyridine solution of diethyl(α-methoxybenzylidene)malonate and *N*-methylhydroxylamine hydrochloride was refluxed 8 hours. the solvent removed, and the ester (4, R = Ph) collected after addition of water, m.p. 138-139° [from ethanol, lit. (5) m.p. 138-139°], yield 85%; nmr (deuteriochloroform): 1.1 (t, 3H), 3.45 (s, 3H), 4.16 (q, 2H), 7.55 δ (m, 5H).

Hydrolysis of the ester was carried out at room temperature during 5 hours in 3% aqueous sodium hydroxide. Acidification gave the acid (5a, R = Ph), m.p. 191-192° dec., from chloroform [lit. (11), 192-193°, from methanol], yield 73%, crude.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N, 6.39. Found: C, 60.50; H, 4.24; N, 6.42.

The acyl chloride (5b, R = Ph) was prepared from the acid with thionyl chloride in refluxing chloroform, m.p. 155-157° (from benzene).

Anal. Calcd. for $C_{11}H_8ClNO_3$: C, 55.59; H, 3.40; Cl, 14.91; N, 5.89. Found: C, 55.54; H, 3.31; Cl, 14.33; N, 6.02.

The amide (5d, R = Ph) was obtained by treatment of the chloride with concentrated aqueous ammonium hydroxide, m.p. 194-195° (from ethanol), yield 95%.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.76; H, 4.98; N, 12.85.

2-Methyl-3-phenylisoxazolin-5-one from 2-Methyl-3-phenyl-4-carboxyisoxazolin-5-one (5a, R = Ph).

The acid (5a, R = Ph) was heated at 175° until gas evolution ceased. The residue was then dissolved in ether, washed with dilute aqueous sodium hydroxide, and recrystallized from petroleum ether after removal of the ether, m.p. 43-45°. The product was identic to an authentic sample of 2-methyl-3-phenylisoxazolin-5-one (2).

Pharmacological Tests.

Albino rats of Wistar strain were treated with a saline solution of 2,4-dimethylisoxazolin-5-one 3-carboxy(*N*,*N*-diethyl)amide. All animals treated underwent a convulsive symptomatology characterized by tonic-clonic episodes. The compound was active by both gastric and intraperitoneal route. The minimal convulsant dose by intraperitoneal route was ca. 0.2 mg./kg. of body weight.

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