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2-METHYLISOXAZOLIN-5-ONES—I

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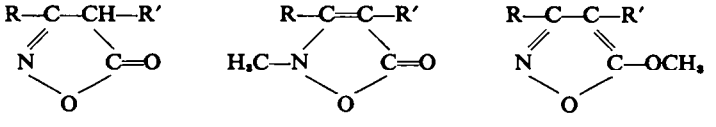
Abstract—N-methylisoxazolin-5-ones were obtained, in addition to the isomeric 5-methoxy-isoxazoles, by methylation of isoxazolin-5-ones or, through a more direct way, by reaction of N-methylhydroxylamine on β-oxoesters. The structures assigned are proved by catalytic hydrogenation or by alkaline hydrolysis (see next paper). Bromination of both 3-phenyl and 4-phenyl compounds by N-bromosuccinimide is described. Some remarkable differences between physical properties of 3-aryl and 4-aryl compounds in the solid phase are pointed out.

Two routes have been attempted for the synthesis of 2-methylisoxazolin-5-ones (II): (1) methylation of isoxazolin-5-ones (I) with various reagents; (2) reactions of N-methylhydroxylamine with β-oxoesters.

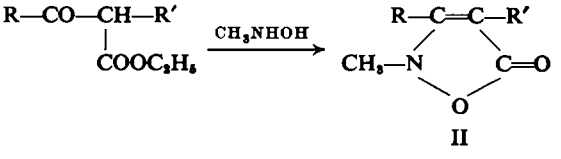
The first method yields N-methyl (II) or O-methyl (III) derivatives, or both; the relative amount of II and III depending on the nature of the substituents R and R',



I II III

and sometimes on the reagent employed. In some cases one of the two isomers was not detected (Table 1). When mixtures are obtained, it is in general possible to separate the two isomers on the basis of the larger volatility of the O-methyl derivative (III) or the lower solubility in ether of the N-methyl derivative (particularly in the case of 4-phenyl compounds). Some isoxazolin-5-ones, namely the methyl compounds, are not easily obtainable, or are not known.

The second method, affording directly the title compounds, has been previously reported for the synthesis of the 2,3,4-trimethylisoxazolin-5-one[6] and of two ethoxy-carbonyl derivatives.[9] This general method (a) is the most convenient. Compounds II



II

[1] A. R. Katritzky, S. Øksne and A. J. Boulton, *Tetrahedron* **18**, 777 (1962).
[2] F. De Sarlo, *Tetrahedron* in press.
[3] E. Olivieri-Mandalà and A. Coppola, *Rend. Acc. Lincei* [5] **20**, I, 244 (1911).
[4] P. Grünanger and M. R. Langella, *Gazz. Chim. Ital.* **89**, 1784 (1959).
[5] Unpublished research.
[6] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).
[7] E. P. Kohler and A. H. Blatt, *J. Amer. Chem. Soc.* **50**, 504 (1928).
[8] R. Scarpati and G. Speroni, *Gazz. Chim. Ital.* **89**, 1511 (1959).
[9] H. Ulrich, J. N. Tilley and A. A. Sayigh, *J. Org. Chem.* **27**, 2160 (1962).

Table 1.—Methylation of isoxazolin-5-ones (I).

R	R′	Methylating agents	Yield %	Relative amount of derivatives II	Relative amount of derivatives III	Refs
CH_3	H	CH_3N_2	22	1/2	1/2	1
CH_3	CH_3	CH_3N_2	75	1/3	2/3	2
C_6H_5	H	Ag salt + CH_3I				
		$CH_3OH + H_2SO_4$	20	0	1	3, 4
		CH_3N_2	99			
H	C_6H_5	CH_3N_2	92	1/3	2/3	5
C_6H_5	CH_3	$C_2H_5ONa + CH_3I$	73	1	0	6
CH_3	C_6H_5	CH_3N_2	96	1/7	6/7	
C_6H_5	C_6H_5	$CH_3ONa + CH_3I$	57*	1	0	7
		CH_3N_2	28	0	1	8

* 34% of the isoxazolin-5-one being recovered unchanged.

with no substituents in 4 (R′ = H) can also be obtained by addition of N-methylhydroxylamine to the derivatives of the propiolic ester (method b). In one case (II: R = H, R′ = CH_3), the synthesis was successful starting from methyl α-methyl-β-methoxy-acrylate (method c). Both the methods (b) and (c) give lower yields than method (a).

The compounds prepared are listed in Table 2, with their respective m.ps and preparative methods. Method (a) is generally applicable if pyridine is used as solvent, although both reactivity and yield depend upon the nature and the position of the substituents on the oxoesters; in ethanol lower yields were observed (last columns of Table 2).

Table 2.—2-methylisoxazolin-5-ones (II).

n	R	R′	M.p.	Methods of prep.	Yields of method (a) in pyridine	Yields of method (a) in alcohol
IV	CH_3	H	41–42°	a, b	50–60%	0
V	H	CH_3		a, c	37%	21%
VI	CH_3	CH_3	39–40°	a	78%	25%
VII	C_6H_5	H	43–45°	a, b	52%	0
VIII	H	C_6H_5	144–146°	a	89%	60%
IX	CH_3	C_6H_5	112–113°	a	91%	73%
X	C_6H_5	CH_3	67–69°	a	56%	5·8%
XI	C_6H_5	C_6H_5	102–104°	a	55%	65%

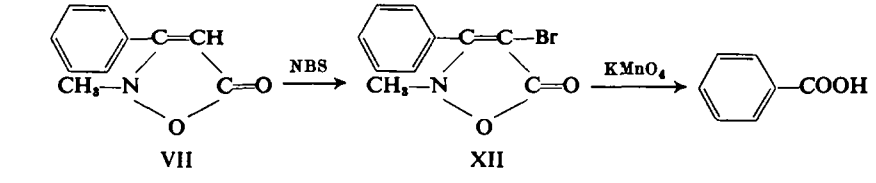
IV Also prepared from N-methylhydroxylamine and diketene (yield 67%) or by methylation of 3-methylisoxazolin-5-one.[1]

VI By using alcohol as solvent, added of AcOH, the yield was 68%.[6]

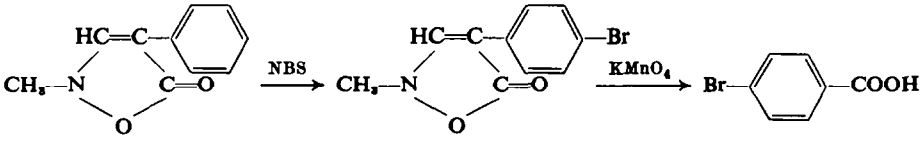
X Obtained by methylation of 3-phenyl-4-methylisoxazolin-5-one with CH_3I.[6]

The formation of 1,3,5-trimethyl-2,4-dicarbethoxypyrrole as a by-product in the reaction between acetoacetic ester and N-methylhydroxylamine might be due to the existence of a competitive reaction in which the first product between N-methylhydroxylamine and acetoacetic ester condenses with another molecule of ester instead of undergoing an intramolecular cyclization. However the amount of the by-product does not increase appreciably even if a large excess of acetoacetic ester is employed.

By action of N-bromosuccinimide on VII and VIII, good yields of the bromoderivatives XII and XIII are obtained. Their structures were confirmed by the analysis of the products obtained by oxidative decomposition:



VII XII



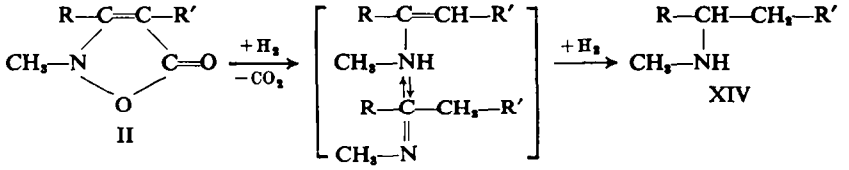
VIII XIII

Compound XII is identical with the product obtained by Katritzky *et al.* by methylation of 3-phenyl-4-bromoisoxazolin-5-one.[6] Moreover, the presence of bromine on the heterocyclic ring is confirmed by the absence in the NMR spectrum of the peak due to the hydrogen of this ring. This peak is observed in the spectrum of VII.

The structure of the bromoderivative XIII is also confirmed by the nature of the products obtained on alkaline hydrolysis.*

Bromination with N-bromosuccinimide indicates a high electronic density in position 4, as expected on the basis of the mesomeric structures. When that position is occupied by a phenyl group, the electronic charge is localized mainly on the *para* position of such a group, thus allowing *para* bromination by N-bromosuccinimide. This happens, in absence of acid catalysis, only in the case of strongly activated positions.[10]

In anhydrous alcohol,† with Raney nickel, compounds VI, IX, X absorb two moles of hydrogen: through decarboxylation, the secondary amines XIV are obtained:



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* Part II, *Tetrahedron* **22**, 2995 (1966).

† In 95% alcohol, with Pd black as catalyst, compound VI absorbs only one mole of hydrogen, since the intermediate methylimine is hydrolysed to methylethylketone and methylamine.

[10] N. P. Buu-Hoï, *Liebigs Ann.* **556**, 1 (1944); L. Horner, E. Winkelmann, K. H. Knapp and W. Ludwig, *Chem. Ber.* **92**, 288 (1959).

It is interesting (Table 3) that N-methyl-4-arylisoxazolin-5-ones have higher m.ps and lower solubility in ether than the isomeric 3-aryl compounds. Moreover, the

TABLE 3.—PHYSICAL PROPERTIES OF 3-ARYL AND 4-ARYL 2-METHYLISOXAZOLIN-5-ONES.

Compounds II			Solubility in ether at 18°	$\nu_{C=O}$ (cm^{-1})		Dipole moments in benzene soln
R	R'	M.p.	(mg/ml)	solid	CCl_4 sol.	(Debye)
C_6H_5	H	43–45°	160	1743 (1718)*	1751	6·00
C_6H_5	CH_3	67–69°	130	1730	1745	5·73
C_6H_5	Br	108–109°	26	1745 (1738)*	1760	6·20
H	C_6H_5	144–146°	1·5	1700 (1735)*	1758	5·40
CH_3	C_6H_5	112–113°	4·2	1706 (1688)*	1742	5·65
H	*p*-Br–C_6H_4	173–174°	1·4	1680	1760	5·83

* shoulder.

$\nu_{C=O}$ in the solid phase is located before 1706 cm^{-1} for 4-aryl compounds and after 1730 cm^{-1} for all other N-methylisoxazolin-5-ones. It must be noted, however, that these differences are observed only in the solid phase, whereas comparable values are found in solution: e.g. the IR spectra in CCl_4 and the dipole moments in benzene solution. Analysis of the crystal structure should indicate the reason for these differences.

EXPERIMENTAL

2,3-*Dimethylisoxazolin-5-one* (IV). Ethyl acetoacetate in anhydrous pyridine was heated with N-methylhydroxylamine hydrochloride at 100° for 8 hr. Evaporation under vacuum gave a residue which was treated with sat. K_2CO_3aq until slightly alkaline, and then extracted with ether. The residue of the ethereal soln was fractionally distilled, to yield IV, b.p. 88–89°/0·2 torr (102–104°/0·6 torr). It solidified by cooling: m.p. 41–42° (from ligroin). The IR spectrum agrees with the spectral data reported by Katritzky.[1] It is soluble both in water and ether. The best yield (60% on the basis of the N-methylhydroxylamine) was achieved by using an excess of the ester (2·5 moles) for 1 mole of the hydrochloride. By extracting the dark tarry residue after distillation with ligroine, a small amount of 1,3,5-*trimethyl*-2,4-*dicarboethoxypyrrole* was obtained: m.p. 114° (MeOH). Its m.p. and IR spectrum were identical to those of a sample prepared according to the literature.[11] Compd IV was also prepared, although in lower yield, starting from ethyl tetrolate and N-methylhydroxylamine in pyridine, and proceeding as previously described. When anhydrous EtOH was used as solvent, ethyl acetoacetate and N-methylhydroxylamine hydrochloride did not yield appreciable amounts of IV or pyrrole.

2,4-*Dimethylisoxazolin-5-one* (V). Reaction between ethyl formylpropionate (0·1 mole) and N-methylhydroxylamine (0·12 mole) was carried out as described for IV. The fraction boiling at 65–66°/0·2 torr (98–102°/1·5 torr) was collected, yield ca. 37%, colourless, $n_D^{25°} = 1{\cdot}490215$, soluble both in water and ether. Anhydrous EtOH can also be employed as reaction solvent (yield 21%). Compound V was also prepared starting from the methyl ester of α-methyl-β-methoxyacrylic acid, under similar reaction conditions (yield 30%). (Found: C, 52·71; H, 6·34; N, 12·06. Calc. for $C_5H_7NO_2$ (113·1): C, 53·09; H, 6·24; N, 12·38%.)

2,3,4-*Trimethylisoxazolin-5-one* (VI). The reaction between ethyl α-methylacetoacetate (0·1 mole) and N-methylhydroxylamine hydrochloride (0·12 mole) in anhydrous pyridine, yielded, after evaporation of the ethereal solution, an oily residue which solidified on cooling, m.p. 34–38°; yield 78%. The product was purified by recrystallization from ligroin or pet. ether (m.p. 39–40°). It was soluble both

[11] S. F. MacDonald, *J. Chem. Soc.* 4180 (1952); A. H. Corwin and W. M. Quattlebaum, *J. Amer. Chem. Soc.* **58**, 1081 (1936).

in water and ether. In anhydrous alcohol, as reaction solvent, the yield was 25%; by adding AcOH Katritzky *et al.*[6] obtained a yield of 68%.

Hydrogenation of VI. A 10% soln of VI in anhydrous EtOH was shaken under a 3–4 atm. H_2 press, with Raney Ni as catalyst. An amount of H_2 corresponding to two moles was absorbed in 2–3 days. The soln was filtered and acidified with conc. HCl, and the alcohol evaporated together with most of the water. The residue was made alkaline and the amine steam distilled (XIV, R = R′ = CH_3) and purified as described in the literature,[12] yield 54%. In 95% EtOH, with Pd as catalyst, one mole H_2 was absorbed by IV during 1 hr. From the filtered soln methylethylketone was obtained.

2-Methyl-3-phenylisoxazolin-5-one (VII). A mixture of ethyl benzoylacetate (0·1 mole) and N-methylhydroxylamine hydrochloride (0·12 mole) in anhydrous pyridine was heated on a water bath for 8 hr. After cooling, 2N NaOH (50 ml) was added, and the mixture extracted several times with ether. The ethereal solution was washed until neutral, dried and the solvent removed. Fractional distillation gave VII (b.p. 110°/0·15 torr; 152°/0·5 torr). It solidified on cooling and crystallized from ligroin as white tablets, m.p. 43–45°, yield 52%, insoluble in water, soluble in the common organic solvents and in conc. HCl. By using alcohol as solvent the yield was considerably reduced. Compound VII can also be prepared from ethyl phenylpropiolate and free N-methylhydroxylamine, in alcohol. After heating for 6 hr, the solvent was evaporated and the product purified as reported. In this case the yield was lower. (Found: mol. wt. 175 (Rast); C, 68·54; H, 5·08; N, 8·05; calc. for $C_{10}H_9NO_2$ (175·2): C, 68·56; H, 5·18; N, 8·00%.)

Bromination of VII: *2-methyl-3-phenyl-4-bromoisoxazolin-5-one* (XII). Compound VII was brominated with a small excess of N-bromo-succinimide in boiling anhydrous benzene. The residue, obtained by evaporating the solvent, was washed with water and recrystallized several times from EtOH; m.p. 108–109°, yield ca. 80%. The same product has been obtained by methylation of 3-phenyl-4-bromoisoxazolin-5-one.[6] By heating with $KMnO_4$ in dil NaOHaq, XII yields benzoic acid.

2-Methyl-4-phenylisoxazolin-5-one (VIII). A solution of ethyl formylphenylacetate (0·1 mole) and N-methylhydroxylamine hydrochloride (0·12 mole) in anhydrous pyridine (230 ml) was heated on a water bath for 6–7 hr. After evaporation of the solvent, the residue was treated with water, filtered off and washed. The crude product (16 g) was recrystallized from EtOH, m.p. 144–146°; yield 14·5 g (89%). It is slightly soluble in ether, insoluble in cold alkaline solns and dil. acids and soluble in conc. HCl. The reaction can also be carried out in anhydrous alcohol, but in this case the yield is lower (60%). (Found: mol. wt. 184 (Rast); C, 68·27; H, 5·07; N, 8·06; calc. for $C_{10}H_9NO_2$ (175·2): C, 68·56; H, 5·18; N, 8·00%.)

Bromination of VIII: *2-methyl-4-(p-bromophenyl)isoxazolin-5-one* (XIII). Compound VIII was brominated, m.p. 173–174° (EtOH), yield 83%. (Found: C, 46·90; H, 3·00; Br, 30·68; N, 5·53; calc. for $C_{10}H_8BrNO_2$ (254·1): C, 47·27; H, 3·17; Br, 31·45; N, 5·51%.)

Compound XIII was oxidized with $KMnO_4$ in boiling water; acidification of the filtered solution gave *p*-bromobenzoic acid: m.p. 249–250° (EtOH).

2,3-Dimethyl-4-phenylisoxazolin-5-one (IX). Ethyl α-phenylacetoacetate (0·1 mole) and N-methylhydroxylamine hydrochloride (0·15 mole) in anhydrous pyridine (100 ml) were heated at 100° for 12 hr. The residue after evaporation of the solvent was washed with ether, then with water, yield 91%; m.p. 112–113° (ligroin). In alcohol, as reaction solvent, the yield was 73%. (Found: C, 69·98; H, 5·67; N, 7·62; calc. for $C_{11}H_{11}NO_2$ (189·2): C, 69·83; H, 5·86; N, 7·40%.)

Methylation of 3-methyl-4-phenylisoxazolin-5-one. 3-Methyl-4-phenylisoxazolin-5-one[13] in ethereal suspension was methylated with diazomethane. The ethereal solution was concentrated and the precipitate (mainly IX) collected; complete evaporation of the solvent gave mainly O-methyl derivative. Further purification from ether gave ca. 14% N-methyl (m.p. 111–113°) and ca. 82% O-methyl derivative (m.p. 47–48°, from MeOH). Analysis of the 3-methyl-4-phenyl-5-methoxyisoxazole: (Found: C, 70·07; H, 6·03; N 7·05; OCH_3, 16·22; calc. for $C_{11}H_{11}NO_2$ (189·2): C, 69·83; H, 5·86; N, 7·40; OCH_3, 16·40%.)

Hydrogenation of IX. A soln of IX (0·02 moles) in 150 ml anhydrous EtOH was shaken for 1 day under a 3–4 atm. H_2 press, with Raney Ni. After the absorption of 0·04 moles H_2, the soln was

[12] K. Löffler, *Ber. Dtsch. Chem. Ges.* **43**, 2041 (1910).
[13] W. Logemann, L. Almirante and L. Caprio, *Chem. Ber.* **87**, 1175 (1954).

filtered and fractionated to isolate XIV ($R = CH_3$, $R' = C_6H_5$); b.p. 38°/0·3 torr; 208°/750 torr; m.p. of the hydrochloride 129–134°.

2,4-*Dimethyl*-3-*phenylisoxazolin*-5-*one* (X). Ethyl α-benzoylpropionate (0·1 mole) and N-methylhydroxylamine hydrochloride (0·12 mole) in anhydrous pyridine were heated at 50–60° for 8 hr. The residue after removal of the solvent was treated with 2N NaOH (15 ml). After cooling crude X precipitated (56%); m.p. 67–69° (from ligroin or pet. ether). It is insoluble in water, alkaline hydroxides and even conc acids but soluble in the common organic solvents. A lower yield (5·8%) was obtained by using alcohol as reaction solvent instead of pyridine. (Found: C, 69·98; H, 5·77; N, 7·42; calc. for $C_{11}H_{11}NO_2$ (189·2): C, 69·83; H, 5·86; N, 7·40.)

Hydrogenation of X. Compound X was hydrogenated as for IX. The amine distilled at 93–94° 18 torr. The IR spectrum was identical with that of XIV ($R = C_6H_5$, $R' = CH_3$), prepared as reported in the literature.[14]

2-*Methyl*-3,4-*diphenylisoxazolin*-5-*one* (XI). (1) Methylation of 3,4-diphenylisoxazolin-5-one, according to Kohler and Blatt,[7] gave only XI. It was found however that the m.p. is 102–104° (EtOH) instead of 92°, as reported.[7] Methylation of the same isoxazolin-5-one with CH_2N_2 in benzene is reported[8] to give only the O-methyl derivative. We have found that, if the reaction is carried out in ether, a small amount of N-methyl derivative is obtained in addition to the O-methyl.

(2) A mixture of ethyl phenylbenzoylacetate and N-methylhydroxylamine (molar ratio 1:1·6) in anhydrous pyridine was heated at 90° for 56 hr. After removal of the solvent, the residue was washed with 8% NaOH and filtered off. From alcohol, 55% of product m.p. 95–101° was obtained: after recrystallization, m.p. 102–104°. The same reagents, by refluxing in EtOH for 5 days gave 65·5% of a product m.p. 98–102°. (Found: C, 76·46; H, 5·36; N, 5·81; calc. for $C_{16}H_{13}NO_2$ (251·3): C, 76·48; H, 5·21; N, 5·75%.)

[14] M. Busch and L. Leefhelm, *J. prak. Chem.* 77, 21 (1908).