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STUDIES IN THE CHEMISTRY OF 3- AND 5-ISOXAZOLONES

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Abstract—The unique infra-red carbonyl absorption changes which are observed when an electron-attracting group is attached to the ring nitrogen atom of 5-amino-3-isoxazolones is shown to be independent of the presence of the 5-amino group and characteristic of the 3-isoxazolone system itself; however, it is shown to be dependent on the nature of the substituent at the 4-position. A novel synthesis of the previously unknown unsubstituted 3-amino-5-isoxazolone is also described. The IR spectra of several new 3- and 5-isoxazolones are interpreted in part.

RECENTLY, it was discovered[1,2] that the 3-isoxazolone ring possesses an unusual electronic tractability seemingly dependent upon the nature of the ring nitrogen substituent. This is apparent in a comparison of the IR absorption spectra of the parent compounds (I; R = H) with the 2-sulfonyl derivatives (I; R = SO_2Ar). The arenesulfonyl derivatives absorbed strongly near 1735 cm^{-1} where one would expect

I Ia

absorption by a ring carbonyl of this type to appear. In contrast, the parent compounds (I; R = H) exhibit no absorption in this region; their highest frequency absorption actually being below 1675 cm^{-1}. Moreover, no other tautomeric structure could explain the complete spectra observed.

The parent and the 2-arenesulphonyl derivative both possess the 3-isoxazolone skeleton and, in this sense, are structurally identical; however, the 3-isoxazolone rings are indeed different as evidenced by their IR spectra and must be distinguished. The difference is easily accounted for by a change in the electronic arrangement in the ring and we postulate the parent compound (R = H) be best described by Ia and the arenesulphonyl derivative by I (R = SO_2Ar).[3]

To gain further insight into the nature of the ring system several modifications in the structure are made from previously published series of 5-amino-3-isoxazolones (I; R″ = NH_2, R′ = hydrogen, sec-butyl, cyclohexyl or benzyl).[1,2] In the present

[1] L. Bauer and C. N. V. Nambury, *J. Org. Chem.* **26**, 4917 (1961).
[2] C. L. Bell, C. N. V. Nambury and L. Bauer, *J. Org. Chem.* **26**, 4923 (1961).
[3] In her excellent paper, S. Refn [*Spectrochim. Acta* **17**, 40 (1961)] also showed that 3-substituted 5-pyrazolones, A, absorbed at 1620 cm^{-1} (KBr) and postulated these to exist as the aromatic hybrid (e.g. B or C). However, 3-substituted 4,4-disubstituted-5-pyrazolones, D, absorbed at 1705 cm^{-1} (KBr) and were formulated as lactams. A similar problem confronted D. G. Farnum and P. Yates [*J. Amer. Chem. Soc.* **84**, 1399 (1962)], when they attempted to assign structures to a

TABLE 1. 5-AMINO-3-ISOXAZOLONES,

R	R′	Method of prep.[a]	Solvent of cryst.	Yield, %	M.P.,° (Dec.)	Molecular formula		Analyses C,%	H,%	N,%
iso-C_3H_7	H	A	Ethyl acetate–benzene	46	139–140	$C_6H_{10}N_2O_2$	Calc.	—	—	19·71
							Found	—	—	19·78
iso-C_3H_7	C_6H_5CO	D	Ethyl acetate–benzene	41	159–160	$C_{12}H_{14}N_2O_3$	Calc.	—	—	11·38
							Found	—	—	11·52
iso-C_3H_7	p-$CH_3C_6H_4SO_2$	F	Ethyl acetate–benzene	39	164–165	$C_{12}H_{16}N_2O_4S$	Calc.	—	—	9·45
							Found	—	—	9·63
C_6H_5	H	A	Ethanol	25	184–185	$C_9H_8N_2O_2$	Calc.	61·36	4·57	15·90
							Found	61·55	4·65	15·84

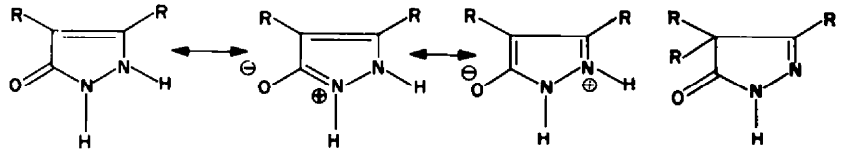
[a] The letters refer to methods of preparation described in reference 1.

TABLE 2. 3-AMINO-5-ISOXAZOLONES

R	R′	Method of prep.[a]	Solvent of cryst.	Yield, %	M.P.,° (Dec.)	Molecular formula		Analyses C,%	H,%	N,%
H	H	—	Ethyl acetate	75	137–138	$C_3H_4N_2O_2$	Calc.	36·03	4·02	28·00
							Found	36·16	4·14	27·92
iso-C_3H_7	H	B	Ethyl acetate	14	160–161	$C_6H_{10}N_2O_2$	Calc.	—	—	19·71
							Found	—	—	19·77
iso-C_3H_7	CH_3CO	C	Benzene	57	137–138	$C_8H_{12}N_2O_3$	Calc.	—	—	15·21
							Found	—	—	15·26
iso-C_3H_7	C_6H_5CO	E	Benzene–cyclohexane	53	103–104	$C_{12}H_{14}N_2O_3$	Calc.	—	—	11·38
							Found	—	—	11·36
iso-C_3H_7	$C_6H_5SO_2$	F	Benzene	57	131–132	$C_{12}H_{14}N_2O_4S$	Calc.	—	—	9·92
							Found	—	—	10·00
C_6H_5	H	B	Ethyl acetate–benzene	54	136–138	$C_9H_8N_2O_2$	Calc.	61·36	4·57	15·90
							Found	61·60	4·55	15·82
C_6H_5	p-$CH_3C_6H_4SO_2$	F	Benzene	73	155–156	$C_{16}H_{14}N_2O_4S$	Calc.	58·19	4·27	8·48
							Found	58·40	4·37	8·44
C_6H_5	p-$CH_3CONHC_6H_4SO_2$	F	Ethanol	60	198–201	$C_{17}H_{15}N_3O_5S$	Calc.	54·69	4·05	11·25
							Found	54·78	4·01	11·26

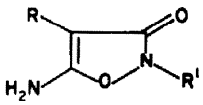
[a] The letters refer to methods of preparation described in reference 1.

series of 5-pyrazolones, A. They found that the 3-phenyl substituted 4-amino-, 4-phenylazo- and 4-diazo-5-pyrazolones absorbed at 1600, 1667 and 1686 cm^{-1} respectively, and described each by



A B C D

aromatic resonance hydrids. (B, C) In view of these observations, it leads us to question the assignment of the 1665–1680 cm^{-1} ($CHCl_3$ solution) band to carbonyl absorption in a series of 1-phenyl-3-methyl-4-phenylazo-5-pyrazolones. [F. A. Snavely, W. S. Trahanasky and F. H. Suydam *J. Org. Chem.* **27**, 994 (1962).]

AND DERIVATIVES, 

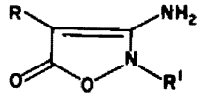
Infra-red Absorption Bands (cm^{-1}) in KBr.

3350 m-b, 3175 m-b, 2960 m, 2920 m, 2770 m-b, 1671 m, 1614 s, 1576 vs-b, 1487 m, 1455 m, 1384 w, 1228 w, 1172 w, 1114 m, 1073 m, 1029 m, 961 m, 883 w, 770 m-b, 706 m.

3400 m, 3280 m-b, 3152 m, 2950 m, 2925 m, 1733 m, 1685 sh, 1627 vs-vb, 1451 m-b, 1304 m-vb, 1265 m, 1157 m-vb, 1098 m-vb, 1021 m-vb, 948 m, 880 w, 806 m, 786 w, 762 m, 722 m, 700 m, 681 m.

3440 m, 3345 m-b, 3160 m, 2960 m, 2925 m, 1733 m-b, 1633 vs-vb, 1594 m, 1580 m, 1441 m-b, 1378 m, 1191 m, 1179 s, 1086 m, 1025 w-b, 985 m-b, 882 m, 813 w-b, 777 w, 706 m.

3500 w, 3250 m-b, 3090 s-vb, 2800 m-b, 1651 sh, 1622 vs-vb, 1585 vs-vb, 1509 s, 1473 m, 1440 m, 1317 w, 1285 w-b, 1237 w-b, 1080 m, 1065 m, 958 m, 882 m-b, 753 m, 717 m.

AND DERIVATIVES, 

Infra-red Absorption Bands (cm^{-1}) in KBr (unless otherwise indicated).

In split mull: 3400 s, 3350 m-b, 3200 m, 2980 w, 2950 w, 1775 vs, 1660 sh, 1633 m, 1600 m, 1482 m, 1370 m, 1199 m-b, 950 m, 931 m, 907 m, 863 m.

3410 vs, 3330 m, 3195 s, 2960 m, 2925 m, 1765 vs, 1642 vs, 1598 s, 1470 m, 1390 w, 1374 w, 1345 m, 1326 vw, 1242 m, 1193 m, 1181 m, 1120 m, 1006 m, 904 vs, 878 m, 694 m-b.

3420 m, 3225 m-b, 3160 m-b, 2965 m, 2925 m, 1741 m, 1607 s, 1616 vs-b, 1583 sh, 1465 m-b, 1386 m-b, 1362 w, 1333 m, 1281 m, 1153 w, 1110 vw, 1074 vw, 1033 vw, 961 m, 822 m, 763 m, 725 m.

3415 m, 3300 m-b, 3215 m-b, 2950 m, 2925 m, 1747 m-b, 1667 s, 1635 vs-b, 1583 w, 1568 m 1452 m, 1379 s, 1351 m, 1281 m, 1197 vw, 1137 m, 978 m, 930 m, 919 m, 876 w, 799 w, 762 m, 705 m.

3455 m, 3355 m, 3190 w, 2950 m, 2920 m, 1759 s, 1660 vs-b, 1604 m, 1583 w, 1450 m-b, 1424 m, 1390 m, 1314 w, 1188 vs, 1086 m, 1033 m, 976 m, 878 m, 777 m, 756 m, 734 m, 698 m.

3450 m, 3340 m-b, 3260 m-b, 3150 m-b, 2760 w-b, 1698 m-b, 1633 vs-b, 1584 vs, 1516 m, 1443 m, 1325 m, 1200 m, 1110 w-b, 1036 w-vb, 964 m, 782 m, 743 m, 713 w.

In split mull: 3460 m, 3350 m-b, 3280 m-b, 3185 m-b, 1750 s, 1630 vs-b, 1598 m, 1506 m, 1447 w, 1430 m, 1375 s, 1307 w, 1278 w-b 1189 s, 1174 s, 1084 m, 1043 w, 945 s, 816 m, 790 m, 780 m, 754 w, 725 m, 678 m.

study the R′ group was simplified to an isopropyl group with the hope that an increase in the clarity of the IR spectra would result. The R′ group is also changed to phenyl which results in a marked alteration of behaviour as reported below. Finally, in order to determine if the unique electronic behaviour of these systems is inherent to only the 5-amino-3-isoxazolones or is characteristic of 3-isoxazolones themselves we sought to examine the structure of some 3-isoxazolones devoid of the 5-amino group.

4-Isopropyl-5-amino-3-isoxazolone. Limiting solubilities of this compound and its acyl and arenesulfonyl derivatives in solvents suitable for IR study prevented us from obtaining clear solution spectra hence only the absorption bands in the solid state are listed in Tables 1 and 2.

Of the five bands listed in the 1400 to 1800 cm^{-1} range, partial deuteration causes the disappearance of only the band at 1614 cm^{-1} with a concomitant appearance of a band at 1521 cm^{-1}. This suggests the amino group hydrogens have exchanged with deuterium and the absorption at 1614 cm^{-1} arises from an NH_2 deformation mode.

In tetrahydrofuran solution a shift of this band from 1616 cm^{-1} to 1497 cm^{-1} is noted. This assignment is further substantiated by the deuteration of another isomer, 4-isopropyl-3-amino-5-isoxazolone. In the solid state spectra the sharp ring C=O band at 1765 cm^{-1} is not affected by partial deuteration but the sharp band at 1645 cm^{-1} is diminished and the strong sharp band at 1595 cm^{-1} is considerably broadened and intensified.

4-Phenyl-5-amino-3-isoxazolone. From the reaction of hydroxylamine with ethyl phenylcyanoacetate we obtained the two isomeric isoxazolones. Interestingly enough, 4-phenyl-5-amino-3-isoxazolone shows a weak but sharp band at 3500 cm^{-1} in its solid state spectra and could indeed be in the 3-isoxazol form. Its highest frequency band in the 1600 cm^{-1} region is at 1651 cm^{-1} and could well be assigned to a ring mode of the 3-isoxazol form. Another unusual feature is that this product could not be induced to give solid acyl or sulfonyl derivatives. The isomeric 3-amino-4-phenyl-5-isoxazolone possesses the usual strong ring C=O band at 1698 cm^{-1} (in KBr; 1736 in acetonitrile) and does form several crystalline sulfonyl derivatives described in Table 2, but fails to yield solid acyl derivatives. The absorption bands of these compounds in the crystalline state are listed in Tables 1 and 2.

In searching the literature, there are few authentic 3-isoxazolones reported[4] but recently several reputed 5-isoxazolones were shown to be actually 3-isoxazolones.[5-7] The isoxazolone originally made by Uhlenhuth[8] from hydroxylamine and ethyl methyl-acetoacetate was shown to be 4,5-dimethyl-3-isoxazolone. This compound was selected as a model compound for our IR study since it lacked the 5-amino group. The IR spectrum in chloroform solution (Table 3) of the above 4,5-dimethyl-3-isoxazolone, two benzoylation products and its benzenesulfonyl derivative were studied and the salient features of each are described and interpreted below.

4,5-Dimethyl-3-isoxazolone and derivatives. The parent compound (I: R = H, R′ = R″ = CH_3) shows only two major absorption bands above 1400 cm^{-1} and below 2000 cm^{-1}. It will be shown that the very intense absorption at 1666 cm^{-1} persists on both N- and O-substitution and hence must be associated with the unperturbed carbon-carbon unsaturation in the ring. Of particular note is the spectrum of 3-methoxy-4,5-dimethylisoxazole[6] which possesses a sharp strong band at 1660 cm^{-1} (in Nujol). By necessity this band must be due to a ring vibration and suggests that in the 3-isoxazolones the 1666 cm^{-1} band is not due to a ring C=O stretching frequency but is also a ring vibration. The second band at 1538 cm^{-1} disappears upon both N- and O-substitution and must be identified with the polar oxygen-carbon-nitrogen atomic grouping. Additional evidence for the assignment is supplied in the hydrogen stretching region which shows broad absorption between 2400 cm^{-1} and 3000 cm^{-1} with the rather unique superimposed multimaxima seen in salts of the ammonium and immonium type. No absorption peaks are found above 3000 cm^{-1} where a typical lactam N-H would show absorption. The IR spectrum clearly reveals the inadequacy of using the conventional uncharged resonance form, I, to describe

[4] A. Quilico has reviewed the chemistry of all isoxazolones, in *The Chemistry of Heterocyclic Compounds, Five and Six-membered compounds with Nitrogen and Oxygen* (Edited by A. Weissberger) Vol. 17, Chap. III p. 117. Interscience, New York, N.Y. (1962).

[5] A. R. Katritzky and S. Øksne, *Proc. Chem. Soc.* 387 (1961).

[6] S. Cabiddu, G. Gaudiano and A. Quilico, *Gazz. chim. Ital.* **92**, 501 (1962).

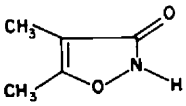
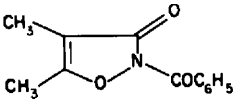
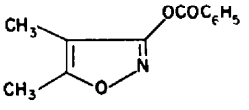
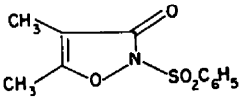
[7] M. Stachel, *Chem. Ber.* **96**, 1088 (1963).

[8] R. von Uhlenhuth, *Liebigs Ann.* **296**, 33 (1897).

the structure of this molecule even when it implies all other forms since, in this instance, the form I contributes in only a minor way to the best description of the molecule.

Benzoylation of 4,5-dimethyl-3-isoxazolone yields two isomeric products the IR spectra of which clearly distinguishes between them. The minor product (4%, m.p. 123–125°) in $CHCl_3$ solution absorbs strongly at 1706 (with a shoulder at 1730) and at 1677 cm^{-1}. On the basis of our experience with the benzoyl derivatives of 5-amino-3-isoxazolones we assign the 1731 cm^{-1} band to a true ring C=O, and that 1706

TABLE 3. INFRA-RED ABSORPTION BANDS (cm^{-1}) OF 4,5-DIMETHYL-3-ISOXAZOLONES AND DERIVATIVES IN CHLOROFORM SOLUTION

			
3000 m-vb	2925 vw	2925 vw	2925 vw
2580	2860 vw	2860 vw	2860 vw
	1731 sh	1759 s-b	1724 s-b
	1706 vs-b		
1666 s	1677 vs	1652 m	1666 s
	1604 m	1600 m	
1538 vs-b		1492 m	
		1470 m	
1440 w	1451 m	1452 m	1450 m
1394 m	1407 m	1394 w	1399 s-b
1358 m	1366 m		
	1348 m	1314 w	1343 m
1252 s	1269 vs-b	1253 vs-b	
	1198 s-b	1179 m	1202 vs-b
1133 m	1140 m	1122 s	
		1074 w	1097 s-b
1042 w		1053 s	
	977 m	1024 m	958 m-b
935 m-b	931 m	934 w-b	
	919 m	861 w-b	

cm^{-1} to the benzamide C=O. The 1677 cm^{-1} band is the previously mentioned high frequency ring mode absorption. This isomer we would then describe by using I, where R = COC_6H_6 and R′ = R″ = CH_3. The major product (74%; m.p. 36–38°) uniquely exhibits a very strong band at 1749 (in $CHCl_3$) accompanied only by a rather weak band at 1655 cm^{-1} in the region above 1600 cm^{-1}. The high frequency band is usually associated with benzoate esters and this abundant isomer is undoubtedly 3-benzoyloxy-4,5-dimethylisoxazole.[9]

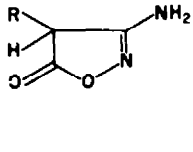
The benzenesulphonyl derivative of I (R = $C_6H_5SO_2$; R′ = R″ = CH_3) also exhibits only two strong absorption bands above 1450 cm^{-1} in chloroform solution. The first at 1724 cm^{-1} can only be a true carbonyl absorption and the second at 1666 cm^{-1} follows the previous assignment as ring mode.

[9] H. Stachel[7] also observed that benzoylation of 5-phenyl-3-isoxazolone yielded 3-benzoyloxy-5-phenylisoxazole (IR band at 1753 cm^{-1} in KBr) however acetylation proceeded at the ring nitrogen atom to give 2-acetyl-5-phenyl-3-isoxazolone (ring C=O at 1715, amide C=O at 1705 cm^{-1} in KBr.)

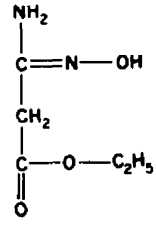
During the progress of this work, there appeared the synthesis of a number of 2-methyl-3-isoxazolones, viz., 2,4,5-trimethyl- and 2-methyl-5-phenyl-3-isoxazolones. Both of these 3-isoxazolones possess the highest frequency band in their IR spectra at 1660 cm^{-1} (strong; in Nujol).[6] Apparently these compounds are best depicted by the bipolar aromatic structure Ia (with their respective substituents).

It appears that the bipolar form Ia, in which the molecule gains aromatic ring stabilization energy is normally the major contributing form for the structure. Only by substituting a strong electron attracting group on the ring nitrogen, such as an acyl or arenesulphonyl group, so that a competing demand for electrons is present, does the major contribution revert from the polarized form Ia to the uncharged form I (in which aromaticity is thought to be lost). This behaviour is reasonable if the ring nitrogen atom changes hybridization upon substitution with electron attracting groups. These phenomena described above are similar to those observed previously[2] for the parent 5-amino-3-isoxazolones and their sulfonyl derivatives. This establishes that this unique behaviour is not dependent upon the presence of the amino group but, on the contrary, the presence of the amino group seems only to obscure the described changes.

In the previous study[1] of the synthesis of the isomeric aminoisoxazolones, the general methods which we developed did not yield the parent 3-amino-5-isoxazolone (II; R = H). Further investigation led us to a novel synthesis of this unsubstituted member of the series. The reaction of ethyl cyanoacetate with hydroxylamine had previously yielded a red gum. From this gum crystalline 2-carbethoxyacetamidoxime (III) is isolated which is cyclized by sodium hydroxide to the previously elusive parent II (R = H). The 5-isoxazolone structure of this parent is evident from the strong band at 1775 cm^{-1} (Nujol) which represents the ring C=O band.[2,10] Other bands (Table 2) in the 1500–1700 cm^{-1}, as well as 3000–3500 cm^{-1} regions resembles those featured in the 4-substituted parents previously described.[2] Attempts to prepare crystalline acyl and sulfonyl derivatives of II (R = H) failed.



II



III

EXPERIMENTAL[11]

4,5-Dimethyl-3-isoxazolone. This compound was prepared in 50% yield from ethyl α-methylacetoacetate and hydroxylamine by the method of Uhlenruth.[8]

2-Benzenesulfonyl-4,5-dimethyl-3-isoxazolone. A mixture of 4,5-dimethyl-3-isoxazolone (1.13 g; 0·01 mole) and benzenesulfonyl chloride (1·16 g) in pyridine (12 ml) was warmed on a steam bath for 0·75 hr. The solution was poured into conc HCl (15 ml) in 100 ml ice-water. The solid which

[10] Other 5-isoxazolones show a similar C=O band: A. R. Katritzky, S. Øksne and A. J. Boulton, *Tetrahedron* **18**, 777 (1962).

[11] All m.ps. are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois, and Dr. Kurt Eder, Geneva, Switzerland. IR spectra were obtained using a Beckman IR-4 spectrometer with NaCl optics.

formed crystallized from benzene and pet ether (b.p. 30–60°), m.p. 128–129°, 0·3 g (12%). (Found: C, 52·37; H, 4·54; N, 5·62, Calc. for $C_{11}H_{11}NO_4S$: C, 52·17; H, 4·37; N, 5·52%).

2-Benzoyl-4,5-dimethyl-3-isoxazolone and 3-benzoyloxy-4,5-dimethylisoxazole. To an ice-cold solution of 4,5-dimethyl-3-isoxazolone (2·26 g; 0·02 mole) in pyridine (?4 ml) was added benzoyl chloride (2·8 g; 0·02 mole) in pyridine (6 ml) during 0·25 hr. The mixture was then kept at 25° for 2·5 hr and subsequently poured onto ice cold dil HCl (1:3; 160 ml). The solid (3·45 g; m.p. 30–38°) was filtered off, dried and dissolved in benzene (20 ml). Addition of pet ether (b.p. 30–60°) yielded colourless needles which recrystallized from the same solvent mixture, m.p. 123–125°, 0·175 g (4% yield). (Found: C, 66·47; H, 4·97; N, 6·23. Calc. for $C_{12}H_{11}NO_3$: C, 66·35; H, 5·10; N, 6·44%).

Slow evaporation of the benzene–pet ether mother liquor afforded a viscous oil which solidified and crystallized from pet ether (b.p. 30–60°) containing a little benzene, m.p. 36–38°, 3·2 g (74%). (Found: C, 66·13; H, 5·12; N, 6·32. Calc. for $C_{12}H_{11}NO_3$: C, 66·35; H, 5·10; N, 6·44%).

Aminoisoxazolones described in Tables 1 and 2. The isopropyl series was obtained starting from ethyl isopropylcyanoacetate,[12] the phenyl series from ethyl phenylcyanoacetate.[13] The isomeric parent compounds and their derivatives were obtained by the methods described previously.[1] The notable exception was that of 3-amino-5-isoxazolone which is described below.

2-Carbethoxyacetamidoxime. Ethyl cyanoacetate (11·30 g; 0·1 mole) was added to an ethanolic solution of hydroxylamine (from 7·70 g hydroxylamine hydrochloride and an equivalent amount of sodium ethoxide) and the solution was warmed at 65–75° for 2 hr. The ethanol was then removed *in vacuo*. The residual red oil was washed with five 50 ml portions pet ether (b.p. 30–60°) and then extracted with five 100 ml portions anhydrous ether. (The residue after the extraction was the α-amidoxime hydroxamic acid $CH_2[C(=NOH)NH_2]CONHOH$.[1] The ether extract was concentrated *in vacuo* to a small volume (25 ml), and the product allowed to crystallize. Careful recrystallization from benzene afforded small colorless needles (7·5 g; 51%) m.p. 62°. (Found: C, 41·33; H, 6·89; N, 19·32. Calc. for $C_5H_{10}N_2O_3$: C, 41·10; H, 6·89; N, 19·17%).

The product deteriorated rapidly on storage at room temp and coalesced to an intractable olack gum within two days.

2-Carbethoxyacetamidoxime hydrochloride was prepared by treating the base in chloroform with dry HCl gas. The oil which was formed crystallized from acetonitrile in colourless prisms, m.p. 105°. (Found: C, 33·15; H, 5·98; N, 15·19. Calc. for $C_5H_{11}ClN_2O_3$: C, 32·89; H, 6·07; N, 15·33%).

Although considerably more stable at room temp than the free base, successive crystallization induced considerable colouring of the sample, indicative of decomposition during this process.

3-Amino-5-isoxazolone. A solution of 2-carbethoxyacetamidoxime (1·46 g; 0·01 mole) in methanol (10 ml) was heated under reflux in NaOHaq. (0·4 g in 0·5 ml water) for 25 min. The solvents were then removed *in vacuo* and the resulting red viscous oil dissolved in water (2 ml). When this solution was neutralized with conc HCl, the crystalline product (0·7 g; 75%) formed, m.p. 134–136° (dec). (See Table 2 for additional data.)

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[12] This was prepared in 90% yield from acetone and ethyl cyanoacetate by the method of E. R. Alexander and A. C. Cope, *J. Amer. Chem. Soc.* **66**, 886 (1944).

[13] Purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisc.