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ISOXAZOLES—I

3-AMINOISOXAZOLIN-5-ONES AND 5-AMINOISOXAZOLIN-3-ONES

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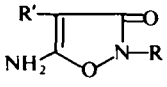
Abstract—IR and UV spectra show that both 5-aminoisoxazolin-3-ones and 2-alkyl-5-aminoisoxazolin-3-ones exist largely in a dipolar form, whereas the 3-hydroxyisoxazole structure for 5-aminoisoxazolin-3-ones is favoured when internal salt formation is feasible.

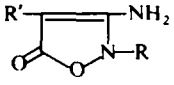
Spectroscopic evidence shows that 3-aminoisoxazolin-5-ones are present either in the 2H or in the 4H form or both. Alkylation of 3-aminoisoxazolin-5-ones in MeOH—K_2CO_3 gives the 2-alkyl derivative, whereas alkylation of the silver salt gives both 2-alkyl and 4-alkyl derivatives.

IR spectra show that 2-dialkylaminoalkyl-3-aminoisoxazolin-5-ones are intramolecularly hydrogen bonded.

IN RECENT years the structure of isoxazolin-3-ones and isoxazolin-5-ones has been fully investigated by means of physico-chemical methods:[1-8] in most cases the structures assigned were based on the IR and UV spectra. In 1961[9,10] the synthesis of 5-aminoisoxazolin-3-ones (I) and 3-aminoisoxazolin-5-ones (II and III)[11] was reported and later a study on their structures, based on the IR spectra, was presented.[10,12a] In the present paper we report and discuss the UV and IR spectra of a further group of aminoisoxazolinones and 2-alkyl-aminoisoxazolinones, whose physical constants and elemental analysis are reported in Table 1. The alkylation of 3-aminoisoxazolin-5-ones will also be discussed and a novel C_4-alkylation reported.



I



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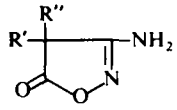

III

[1] A. Quilico and G. Speroni, *The Chemistry of Heterocyclic Compounds*; 5 *and* 6-*membered compounds with Nitrogen and Oxygen* (Edited by A. Weissberger) Vol. 17; Chap V, p. 206. Interscience, New York, N.Y. (1962).

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[9] L. Bauer and C. N. V. Nambury, *J. Org. Chem.* **26**, 4917 (1961).

[10] C. L. Bell, C. N. V. Nambury and L. Bauer, *J. Org. Chem.* **26**, 4923 (1961).

[11] For the sake of simplicity only the most probable of all possible tautomeric formulae is reported.

[12] [a] L. Bauer, C. N. V. Nambury and C. L. Bell, *Tetrahedron* **20**, 165 (1964);
[b] Structure of compound 4 was confirmed by reduction to diethylaminoethylmalondiamide.

TABLE 1

No.	Structure	R	R'	R''	m.p.	Formula	Found N	Req. N
1	I	H	Et	—	145–147°	$C_5H_8N_2O_2$	21·8	21·9
2	I	H	n-Bu	—	134–136°	$C_7H_{12}N_2O_2$	18·0	17·9
3	I	H	Ph	—	164–166°			
4	I	H	diethylamino ethyl	—	164–165°[a]	$C_9H_{17}N_3O_2$	20·8	21·1
5	I	Me	Et	—	172–174°	$C_6H_{10}N_2O_2$	19·8	19·7
6	I	Me	n-Bu	—	75–76°	$C_8H_{14}N_2O_2$	16·4	16·4
7	I	$PhCH_2$	Et	—	99–100°	$C_{12}H_{14}N_2O_2$	12·8	12·8
8	I	3-dimethylaminopropyl	Et	—	98–100°	$C_{10}H_{19}N_3O_2$	19·5	19·7
9	I	Me	Ph	—	165–167°	$C_{10}H_{10}N_2O_2$	14·9	14·7
10	I	3-dimethylaminopropyl	Ph	—	171–173°	$C_{14}H_{19}N_3O_2$	16·2	16·1
11	II	H	Et	—	121–123°	$C_5H_8N_2O_2$	21·7	21·9
12	II	H	n-Bu	—	115–117°	$C_7H_{12}N_2O_2$	17·9	17·9
13	II	H	Ph	—	137–139°[b]			
14	III	H	n-Bu	CH_3	108–110°	$C_8H_{14}N_2O_2$	16·4	16·4
15	III	H	$PhCH_2$	C_2H_5	170–172°	$C_{12}H_{14}N_2O_2$	12·8	12·8
16	III	H	Et	C_2H_5	159–160°	$C_7H_{12}N_2O_2$	17·9	17·9
17	II	Me	Et	—	121–123°	$C_6H_{10}N_2O_2$	21·7	21·8
18	II	Me	n-Bu	—	101–103°	$C_8H_{14}N_2O_2$	16·4	16·4
19	II	Me	Ph	—	206–207°	$C_{10}H_{10}N_2O_2$	14·8	14·7
20	II	$PhCH_2$	Et	—	118–120°	$C_{12}H_{14}N_2O_2$	12·8	12·8
21	II	3-dimethylaminopropyl	n-Bu	—	65–67°	$C_{12}H_{23}N_3O_2$[c] $\cdot H_2O$	16·1	16·1
22	II	diethylaminoethyl	Ph	—	124–126°	$C_{15}H_{21}N_3O_2$	15·2	15·2

[a] Lit.[12] m.p. 184–185. Found: C, 61·4; H, 4·2; N, 16·0. $C_9H_8N_2O_2$ requires: C, 61·3; H, 4·5; N, 15·9%.

[b] Lit.[12] m.p. 136–138°.

[c] Found: C, 65·6; H, 7·7. $C_{12}H_{23}N_3O_2 \cdot H_2O$ requires: C, 65·4; H, 7·7%.

TABLE 2. UV AND IR SPECTRA OF 5-AMINOISOXAZOLIN-3-ONES (I)

No.	R′	R	λ_{max} (mμ)	IR absorption bands (cm^{-1})					
1	Et	H	246[a] 251[b] 240[c]	KBr	3450 s		3100 3000 sb	1630 s	1570 sb
2	n-Bu	H	246[a] 251[b] 240[c]	KBr	3400 s		3100-3000 sb	1630 s	1570 sb
3	Ph	H	252[a] 251[b] 270[c,d]	KBr	3500 mw	3250 ms	3090 3000 sb	1620 sb	1580 sb
4	diethylamino ethyl	H	237[a]	KBr	3380 m		3150 m	1680 s	1470 vs
5	Et	CH_3	250[a]	KBr	3300 —	3100 sb		1650 m	1580 sb
			259[b]	CH_2Cl_2	3500 ms		3400 s	1650 vs	
6	n-Bu	CH_3	252[a]	KBr	3440 s		3160 s	1645 m	1590 sb
			257[b]	CH_2Cl_2	3500 ms		3400 s	1650 vs	
7	Et	$CH_2C_6H_5$	252[a]	KBr	3340 sb		3140 s	1625 vw 1630 m	1570 b
			261[b]	CH_2Cl_2	3500 ms		3400 s	1650 vs	
			265[c]						
8	Et	3-dimethyl-aminopropyl	250[a]	KBr	3300 sb		3150 b	1640 sh	1570 vsb
			259[b]	CH_2Cl_2	3500 ms		3400 s	1640 vs	
9	Ph	CH_3	257[a]	KBr	3340 w		3140 vs	1625 sb	1570 vsb
			257[b]						
			268 and 290sh[c,e]	CH_2Cl_2	3500 ms		3400 s	1650 vs	
10	Ph	3-dimethyl-aminopropyl	256[a]	KBr	3370 s		3100 wb	1650 shw	1575 vsb
			256[b]						
			269 and 290 sh[c,f]	CH_2Cl_2	3490 ms		3400 s	1650 s	

[a] EtOH 95%; [b] 2N HCl-EtOH 95%; [c] 2N NaOH EtOH 95%; [d] log ε = 3·89; [e] log ε = 3·90; [f] log ε = 4·00.
s = strong; b = broad; w = weak; v = very; m = medium; sh = shoulder.

5-Aminoisoxazolin-3-ones

Preparation of 5-aminoisoxazolin-3-ones (Compds 1–10). 5-Aminoisoxazolin-3-ones were prepared from the appropriate cyanoacetate and hydroxylamine, in presence of EtONa as described by Bauer.[9, 12b] Compounds 5, 6 and 9 were similarly obtained by substituting methylhydroxylamine for hydroxylamine. These same products could also be prepared by alkylation of compounds 1, 2 and 3 with MeI and K_2CO_3 in methanol. We have therefore accordingly assigned the above reported structures of 2-alkyl derivatives to the remaining compounds (7, 8 and 10), which were obtained by treatment of compounds 1, 2 and 3 with an alkyl halide in methanol, in presence of potassium carbonate.

UV and IR spectra of 5-aminoisoxazolin-3-ones. In Table 2 we have reported the UV maxima and the most important bands present in the IR spectra (either in KBr or in solution) of compounds 1–10.

UV spectra. The compounds were examined in ethanol and in acid and basic ethanol solution: solubility reasons inhibited the use of less polar solvents such as cyclohexane. In neutral and acid ethanol solution the average log ε for all the compounds was 4·25 ± 0·01. 4-Alkyl-5-aminoisoxazolin-3-ones (Nos. 1 and 2) present in ethanol a

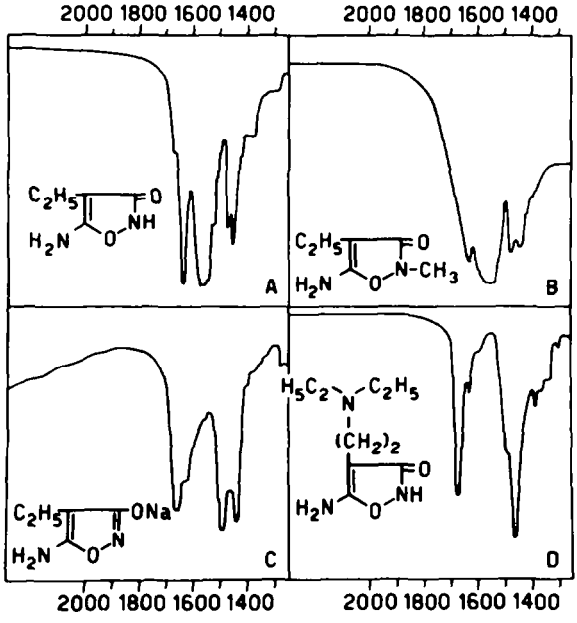


FIG. 1. Spectra of 4-ethyl-5-aminoisoxazolin-3-one (A) and its sodium salt (C); 2-methyl-4-ethyl-5-aminoisoxazolin-3-one (B); 1-diethylaminoethyl-5-aminoisoxazolin-3-one (D).

maximum at 246 mμ which shifts to 251 mμ in HCl ethanol. The corresponding 2-alkyl derivatives (Nos. 5 and 6) have a maximum at 250 mμ which shifts to about 259 mμ in acid solution.

4-Diethylaminoethyl-5-aminoisoxazolin-3-one (No. 4) as well as 3-methoxy-4-ethyl-5-aminoisoxazole[13] present a maximum at 238 mμ. The 4-aryl- derivatives show

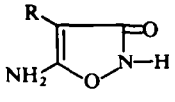
[13] 3-Methoxy-4-ethyl-5-aminoisoxazole was obtained, together with some N-methyl derivative (No. 6), by treatment of compound 1 with diazomethane.

the expected bathochromic shift: 4-phenyl-5-aminoisoxazolin-3-one absorbs at 252 mμ (251 mμ in HCl–EtOH); 2-alkylation (Nos. 9 and 10) shifts the maximum to 257 mμ.

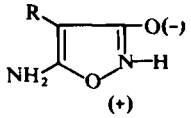
IR spectra. In the solid state the 5-aminoisoxazolin-3-ones (Nos. 1, 2 and 3) exhibit the complex pattern already reported by Bauer[10,12] who assigned the 1630 cm^{-1} band to the NH_2 scissoring mode and the strong broad band at about 1575 cm^{-1} to the C=C and C=N ring vibration. 4-Diethylaminoethyl-5-aminoisoxazolin-3-one presents a different spectrum with two strong bands at 1680 cm^{-1} and 1470 cm^{-1} (broad) (Fig. 1D). 2-Alkylation does not seem to change very much the 6 μ region of the IR spectrum of the parent compound: here also a medium band is present at ca. 1640 cm^{-1} and a very strong one is present at about 1575 cm^{-1} (Fig. 1B). The IR spectra of all the compounds which could be dissolved in dichloromethane (Nos. 5–10) showed, in this solvent, two bands at 3500 and 3400 cm^{-1} which can be assigned to the NH_2 stretching mode: in the 6 μ region a single large and very strong band was present at about 1650 cm^{-1}.

DISCUSSION

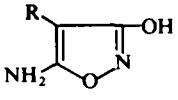
According to Bauer[10,12] 5-aminoisoxazolin-3-ones are best depicted by a resonance hybrid of structures IV and V, V being the largest contributing structure.



IV



V



VI

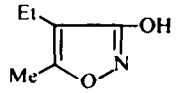
This representation accounts for the absence of the band at about 1670 cm^{-1} (CO lactam stretching) which had been previously found[6,8] to be present in the spectra of simple isoxazolin-3-ones such as 2,4,5-trialkylisoxazolin-3-ones.

The 3-OH tautomer structure VI cannot, however, be ruled out and it has been in fact favoured by Quilico[6b] and Katritzky[8] in the case of 5-alkylisoxazolin-3-ones.

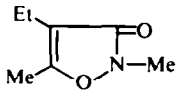
According to our data there is no conflict between these hypotheses and we will here present the evidence that in the case of 5-aminoisoxazolin-3-ones, and owing to the presence of an amino group which can stabilize the positive charge, the contributing structure V of the resonance hybrid IV–V, represents these compounds. We will show also that in certain cases the tautomer 3-hydroxy-5-amino-isoxazole structure VI can become favoured.

The strongest argument in favour of the dipolar structure V is to be found in the spectra of 2-alkyl-5-aminoisoxazolin-3- ones. In fact while the 6 μ region (CO and ring modes) of the spectrum of the model compound 3-hydroxy-4-ethyl-5-methyl-isoxazole (VII) greatly differs from the one of 2,5-dimethyl-4-ethylisoxazolin-3-one (VIII),[6,8] as it is to be expected since 2-alkylation involves a change from a 3-hydroxy-isoxazole to a isoxazolin-3-one structure, no large difference is found between the spectra of 5-aminoisoxazolin-3-ones and their 2-alkyl derivative (e.g. 1 and 5; 2 and 6). The presence in the spectra (solid state) of 2-alkyl-5-aminoisoxazolin-3-ones of strong broad bands at about 1640 and 1580 cm^{-1}, that are also present in the spectra of the

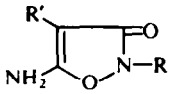
parent 5-aminoisoxazolin-3-ones and which have been assigned to ring vibrations, should be especially noted.



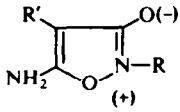
VII



VIII



IX

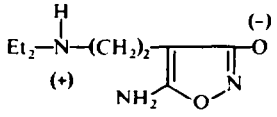


X

The similarity of the spectra and the absence of a CO γ-lactam band can be explained by assigning to 5-aminoisoxazolin-3-ones and to their 2-alkyl derivatives (in the solid state) the analogues hybrid structures IV–V and IX–X, a great weight being given in both cases to the dipolar contributing forms (V and X).

The alkyl derivatives were also examined as dichloromethane or chloroform solutions: in the 3 μ region the presence of the 3500 and 3400 cm^{-1} bands (NH_2 stretching modes) clearly demonstrated that these compounds are present in the amino rather than the imino form. In the 6 μ region, only a single very strong and large band at about 1650 cm^{-1} is left and therefore, in dichloromethane solution, a distinction between IX and X is not feasible. Some information can however be gained from the UV spectra. In acid solution, where the dipolar form should be less favoured, the UV maximum shifts to longer wavelengths and this fact suggests that in ethanol solution X is a contributing form.[14]

The large contribution of V rather than VI to the structure of 5-aminoisoxazolin-3-ones (Nos. 1, 2, 3) has been further substantiated by the preparation of the 4-diethylaminoethyl derivative (No. 4) to which the 3-hydroxy-isoxazole (VI) or better the internal salt like structure XI has been assigned on the following grounds. The



XI

product is insoluble in aprotic solvents but soluble in water and gives a very strong $FeCl_3$ reaction which is an index of an high enol content. The 3 μ region of the IR spectrum presents a weak broad band at 2500–2300 cm^{-1} which is indicative of a salt like structure (XI), in accord with the solubility behaviour. The 6 μ region presents only two bands[15] at 1680 cm^{-1} and 1470 cm^{-1} and it resembles closely the 6 μ region of both 3-hydroxy-4-ethyl-5-methylisoxazole (VII)[6 8] and 4-ethyl-5-amino-

[14] The bathochromic shift (comps 7, 9, 10) in alkaline solution is probably due to the 2,4-dialkyl-3-hydroxy-5-imino-isoxazoline tautomer structure.

[15] The 1570 cm^{-1} (ring vibration) band, which we have related to the dipolar structures V and X, is no longer present.

TABLE 3. UV AND IR SPECTRA OF 3-AMINOISOXAZOLIN-5-ONES (II AND III)

No.	R'	R''	R	λ_{max}(mμ) in EtOH	IR absorption bands (cm^{-1})					
11	Et	--	H	250 log ε 4·19	KBr	3440 m	3360 m	3200 m	1770 s	1635 s	1595 ms
					CH_2Cl_2	3500 m	3400 s		1790 s	1635 sb	
12	n-Bu		H	250 log ε 4·19	KBr	3400 m	3350 m	3200 m	1700 s	1630 s	1590 ms
					CH_2Cl_2	3500 m	3400 s		1790 mw	1725 m	1650 sb
13	Ph	--	H	255 log ε 4·24	KBr	3440 m	3200–2500 b		1700 s	1600 sb	1500 s
					CH_2Cl_2	3500 m	3400 s		1745 s	1660 sb	
14	n-Bu	Me	H	<220	KBr	3440 m	3320 m	3100 m	1770 s	1635 s	1600 m
					CH_2Cl_2	3500 m	3400 s		1790 s	1635 sb	
15	$PhCH_2$	Et	H	245	KBr	3440 m	3380 m	3240 m	1755 s	1630 s	1608 m
					CH_2Cl_2	3500 m	3400 s		1780 s	1635 sb	
16	Et	Et	H	<220	KBr	3440 m	3380 m	3240 m	1780 s	1640 s	1600 ms
					CH_2Cl_2	3500 m	3400 s		1790 s	1640 sb	
17	Et	--	Me	255 log ε 4·25	KBr	3350 m	3180 m		1700 w	1650 s	1575 vs
					CH_2Cl_2	3500 m	3400 s		1735 s	1650 sb	
18	n-Bu		Me	255 log ε 4·24	KBr	3380 m	3180 m		1685 m	1650 s	1575 vs
					CH_2Cl_2	3500 m	3400 s		1740 s	1650 sb	
19	Ph		Me	265 log ε 4·23	KBr	3500 m	3320 m	3180 m	1680 s	1635 s	1550 vsb
					CH_2Cl_2	3500 m	3400 s		1750 s	1650 sb	
20	Et		$PhCH_2$	256 log ε 4·27	KBr	3400 m	3200 m		1690 m	1640 s	1580 sv
					CH_2Cl_2	3500 m	3400 s		1740 s	1650 sb	1605 s
21	n-Bu		3-dimethylamino-propyl	255	KBr	3320 m	3180 m		1720 s	1650 s	1590 s
					CH_2Cl_2	3470 m			1730 s	1640 s	1610 ms
					$CDCl_3$	3480 m	2850 sb				
22	Ph		diethylaminoethyl	268	KBr	3300–2700 sb			1700 s	1660 m	1590 sb
					CH_2Cl_2	3470 m			1730 s	1630–1600 sb	
					$CDCl_3$.	3470 m	2800–2700 sb				

s = strong; b = broad; w = weak; v = very; m = medium.

oxazolin-3-one sodium salt[15] (Fig. 1 C). Furthermore the 3-hydroxyisoxazole rather than the dipolar (V) structure is in better accord with the UV spectrum.[16a]

CONCLUSIONS

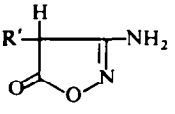
The dipolar structure X is assigned to 2-alkyl-5-aminoisoxazolin-3-ones. 5-Amino-isoxazolin-3-ones are also present in the dipolar (V) rather than the 3-hydroxyisoxazole structure (VI), unless the latter is stabilized by salt formation.[16b]

5-*Aminoisoxazolin-5-ones*

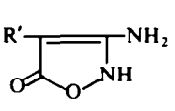
Structure and spectra. Considerable UV and IR spectroscopic data on isoxazolin-5-ones has already been reported and interpreted[1, 3, 5, 17] and it can confidently be used to assign the correct structure to the new compounds of this class. We will therefore present jointly the synthesis and the structural proofs of compounds Nos. 11–22 (reported in Table 1) which will be divided in four sub-groups.

(a) 3-*Amino*-4-R-*isoxazolin*-5-*ones.* Compounds 11, 12 and 13 to which structure XII should have been assigned according to Bauer[10] (cf. however[12]) were obtained by condensation of the appropriate ethyl cyanoacetate with hydroxylamine.[9] The IR spectrum (dichloromethane solution) showed the presence of a NH_2 group, in accord with previous findings[10] and it was eventually used to distinguish between the tautomer formulae XII and XIII.[18] According to the IR spectra, compound 11, in dichloromethane solution, is present in large part in the 4H form (XII); compound 13 is instead present in the 2H form (XIII), whereas the spectrum of compound 12 shows the presence of both the 2H and 4H forms.

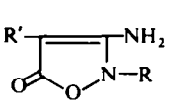
In ethanol solution the equilibrium shifts toward the 2H form. In fact the position of the absorption maximum of the UV spectra of the three compounds require that in ethanol all these compounds be present in part in the 2H form (XIII): from the



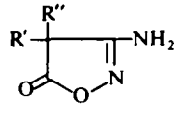
XII



XIII



II



III

[16] [a] Cf. the spectrum of 3-methoxy-4-ethyl-5-aminoisoxazole and the spectra of 4-alkyl-5-aminoisoxazolin-3-ones in alkaline solution;

[b] The NMR spectra have previously[8] been used to confirm the 3-OH structure of isoxazolin-3-ones; in the case of 5-aminoisoxazolin-3-ones, however, the same solvents (CCl_4 or $CDCl_3$) could not be used owing to solubility reasons and we had to employ acetone-d_6 where structure VI should be favoured by hydrogen bonding.

The NMR spectrum in this solvent of 4-ethyl-5-aminoisoxazolin-3-one shows the presence of an NH_2 group (2 protons at 3·80 τ) in accord with the IR spectrum in KBr. Another rather broad signal is present at 0·10 τ and is due to one proton which readily exchanges with water. The value of the chemical shift does not allow a clear-cut distinction between formulae IV–V and V.

2-Methyl-5-aminosoxazolin-3-ones such as 2-methyl-4-ethyl-5-aminoisoxazolin-3-one present in DMSO-d_6 a peak at 2·34 τ (2 protons; NH_2) and a peak at 6·82 τ (3 protons; N—CH_3) as expected.

[17] A. R. Katritzky and J. M. Lagowsky, *Advances in Heterocyclic Chemistry* Vol. II (Edited by A. R. Katritzky) p. 36. Academic Press. New York· N.Y. (1963).

[18] It is known[3] that an isoxazolin-5-one of structure XII should present a CO band at about 1790 cm^{-1} (β,γ-unsaturated-γ-lactone), whereas an isoxazolin-5-one of formula XIII should present a CO band at about 1750–1730 cm^{-1} (α,β-unsaturated-γ-lactone).

values of the extinction coefficient (cf. also compounds 17–20) it is also clear that the 2H form (XIII) is indeed largely preferred.[19a]

(b) 2-*Alkyl*-3-*amino*-4-R-*isoxazolin*-5-*ones*. Condensation of ethyl ethylcyanoacetate with methylhydroxylamine afforded the isoxazolone No. 17 which was found to be an isomer of No. 5 and to which the structure II (R = Me; R′ = Et) was accordingly assigned. The structure was confirmed by the IR spectrum (CH_2Cl_2) which showed the presence of an α,β-unsaturated-γ-lactone type carbonyl band (1740 cm^{-1}). The UV spectrum presented, in comparison with the spectrum of the 2H parent compound No. 11, the expected bathochromic shift and the larger extinction coefficient.

This same product could also be obtained by alkylation of compound 11 with methyl iodide in methanol solution, in the presence of potassium carbonate. This procedure was applied to different 3-amino-4-R-isoxazolin-5-ones (Nos. 11, 12, 13) and to the compounds in this way obtained (No. 17–20) the structure of 2-alkyl derivatives II was accordingly assigned.[19b]

(c) 3-*Amino*-4,4-*dialkylisoxazolin*-5-*ones*. When alkylation of 3-amino-4-ethylisoxazolin-5-one with benzyl bromide was performed on the sodium salt dissolved in dimethylformamide the yields were somewhat lower and a by product could be isolated by chromatography.[20] Its UV spectrum (No. 15) presented only the low benzenoid band and this strongly suggested formula III (R′ = Et; R″ = Ph—CH_2). Moreover the IR spectrum presented, in dichloromethane solution, two bands at 3500 and 3400 cm^{-1} (free NH_2 stretching bands) and a strong band at about 1780 cm^{-1} (CO stretching mode in a 4H-isoxazolin-5-one[3]) which could only be explained by assuming that the isoxazolone had been C-alkylated to give a compound having formula III. An isoxazolinone of formula III (R′ = R″ = Et) was obtained by direct synthesis. Condensation of ethyl diethylcyanoacetate with hydroxylamine and sodium ethylate gave a 4,4-diethyl-aminoisoxazolinone to which the structure of 3-amino-4,4-diethylisoxazolin-5-one (III; R′ = R″ = C_2H_5) rather than 5-imino-4,4-diethylisoxazolin-3-one was assigned since, beside showing no UV absorption, in dichloromethane solution were present the typical bands due to a free NH_2 (3500 and 3400 cm^{-1}) and a CO band at 1790 cm^{-1}. Since the spectra of compounds Nos. 15 and 16 were very close, the structure III previously assigned to No. 15 was confirmed and consequently the occurrence of a C-alkylation reaction in the isoxazolinone field was also proved.[21]

When the silver salt of 3-amino-4-ethylisoxazolin-5-one was treated with benzyl bromide in acetonitrile, C-alkylation and N-alkylation products were formed in

[19] [a] The NMR spectra are in accord with these findings. In acetone-d_6 solution compound 11 presents a triplet centered at 6·37 τ (integration value 0·60 protons). Accordingly, in this solvent, approximately 60% of the 4H form, which gives rise to this signal, is present.

The NMR spectrum of compound 13 shows only the presence of 5-phenyl protons (2·3 2·7 τ, multiplet), $2NH_2$ protons (3·4 τ) and a broad band (1 proton) at about 0·2 τ. Compound 13 is therefore in the 2H form.

The NMR spectrum of 2-methyl-3-aminoisoxazolin-5-ones such as 2-methyl-3-amino-4-ethylisoxazolin-5-one presents the expected peaks at 3·67 τ (2 protons; NH_2) and 6·87 τ (3 protons; N—CH_3). [b] The UV and IR spectra are strictly similar to the one of compound 17 and support these conclusions.

[20] This by-product was eventually found by TLC to be formed in limited yields also when the general procedure was employed.

[21] Although partial C-alkylation of 5-pyrazolones, particularly with benzyl halides,[22] is a long known fact,[23,24] only O- and N-alkylation of isoxazolin-5-ones had been until now reported.[25,26a,26b]

comparable amounts, although the total yield was lower owing to the formation of some tars.[27] Moreover, the use of a silver salt allowed the isolation in limited yields of a C-alkylation product (No. 14) also when a less reactive alkyl halide, such as methyl iodide, was used.[28]

(d) 2-*Dialkylaminoalkyl*-3-*aminoisoxazolin*-5-*ones*. Alkylation of 3-aminoisoxazolin-5-ones with dialkylaminochloroethane or dialkylaminochloropropane in methanol, in presence of K_2CO_3, afforded a dialkylamino alkyl derivative which could not be a C_4 derivative because it had a UV absorption at 255 mμ and a band at 1730 cm^{-1}, already assigned (see 2-alkyl-3-aminoisoxazol-5-ones) to a CO carbonyl in a 2H-isoxazolin-5-one. Since the IR spectrum lacked the typical 3500 and 3400 cm^{-1} bands due to a free NH_2 (only one band being present at 3480 cm^{-1}) it was at first thought it could be a 3-alkylamino derivative but the synthetic procedure suggested the structure of 2-R derivative (II; R = dialkylaminoalkyl). That this was indeed the case was demonstrated by means of a straightforward synthesis of 2-diethylaminoethyl-3-amino-4-phenylisoxazolin-5-one (compound No. 22).

3-Amino-4-phenylisoxazolin-5-one (No. 13) was treated at room temperature with an excess of 1,2-dibromoethane and K_2CO_3 in methanol to give 2-(2-bromoethyl) 3-amino-4-phenylisoxazolin-5-one which showed the expected IR spectrum of a 2-alkyl-3-aminoisoxazolin-5-one and, more important of all, the 3500 and 3400 cm^{-1} bands (free NH_2) were clearly present. This compound was next treated with an excess of diethylamine: bromine substitution occurred easily and the desired 2-diethylaminoethyl-3-amino-4-phenylisoxazolin-5-one was isolated in good yield and found to be identical (TLC, IR and mixed m.p.) with the alkylation product of 3-amino-4-phenylisoxazolin-5-one with diethylaminochloroethane (compd. No. 22).

The IR spectrum[30] of 2-dialkylaminoalkyl-3-aminoisoxazolin-5-ones present the expected 1730 cm^{-1} band (see Section b), but, as we have already remarked, only one band is present, in dichloromethane solution, in the 3 μ region, at 3470 cm^{-1}. However in deuterochloroform[31] a broad and strong absorption band, superimposed on the CH_2 and CH_3 stretching bands, was present at about 2850 cm^{-1} in the case of compound 21 and at 2800–2700 cm^{-1} for compound 22. The features of these spectra can be explained by assuming the formation of an intramolecular hydrogen bond between the NH_2 group and the dialkylamino group. Similar intramolecular bonds between a β amide group and a tertiary nitrogen have been recently studied[32] and it

[22] A. Sonn and W. Litter. *Chem. Ber.* **66**, 1582 (1963).

[23] L. Knorr. *Ber. Dtsch. Chem. Ges.* **28**, 706 (1895).

[24] Usually C-alkylation occurs in absence of solvents and at high temp.

[25] P. Grünanger and M. R. Langella. *Gazz. Chim. Ital.* **89**, 1784 (1959).

[26] [a] A. Mustafa, W. Asker, A. H. Harbash, N. A. L. Kassab and M. H. Elnagdi. *Tetrahedron* **20**, 1133 (1964). [b] F. De Sarlo, L. Fabbrini and G. Renzi, *Tetrahedron* **22**, 2989 (1966).

[27] The oily forerun of the chromatographic columns contained probably the O-alkyl derivative, but, being outside the scope of this work, was not investigated further.

[28] These results apparently contradict Kornblum's rule.[29] which would predict the formation of O- or N-, rather than C-alkyl derivatives. It is, however, possible that in this case the solvent plays a determinant role.

[29] N. Kornblum, R. A. Sunbey, R. K. Blackwood and D. C. Iffland. *J. Am. Chem. Soc.* **77**, 6269 (1955).

[30] The UV spectrum does not differ from the spectra of other 2-alkyl derivatives and needs no comment.

[31] Deuterochloroform was used because of its good solvent properties accompanied by a low absorption at 3 μ.

[32] W. Barbieri and L. Bernardi. *Tetrahedron* **21**, 2453 (1965).

was shown that in those cases in place of the typical 3520 and 3420 cm^{-1} bands (symmetric and antisymmetric amide NH_2 stretching modes), a sharp band was present at 3480 cm^{-1}, accompanied by a broad strong band at about 3200 cm^{-1}. In the present case the association band occurs at lower wavelengths and this could be related to the size of the ring formed in the intramolecular hydrogen bond.[33]

EXPERIMENTAL[35]

M.ps are uncorrected. The IR spectra were recorded on a Perkin-Elmer M 21 spectrometer fitted with NaCl optics or with a Perkin-Elmer M 237 double grating spectrometer. Samples were prepared as solutions in different solvents and examined in 1 mm cells with NaCl windows and as dispersions in pressed KBr discs

4-Diethylaminoethyl-5-aminoisoxazolin-3-one (No. 4)

Diethylaminochloroethane HCl[36] (33 g) was dissolved in EtOH (80 ml) and treated first with EtONa (1 equiv) and next with ethyl cyanoacetate. One equiv EtONa was slowly added to the suspension and at the end the mixture was refluxed for 2 hr. The solvent was eliminated *in vacuo*. the residue was treated with dil HCl (1·3 equiv) and the soln was extracted first with ether and again. after basification with K_2CO_3. with ether. The second ether extract was distilled and 16·5 g of *ethyl 3-diethylaminoethylcyanoacetate* were collected. b.p. 92–95° at 0·5 mm Hg. (Found: N. 13·5. $C_{11}H_{20}N_2O_2$ requires: N. 13·2%). and condensed in MeOH with 1·1 equivs of $NH_2OH \cdot HCl$ and 2·2 equivs of MeONa at 60° for 5 hr After elimination of the solvent the residue was dissolved in H_2O (30 ml) and 1·1 equivs of H_2SO_4 was added. The soln was percolated through Dowes 50 W (H cycle) and discarded. The resin was eluted with dil NH_4OH: evaporation of the solvent left an oil which crystallized from EtOH–MeOH to give compound No. 4 (7·5 g).

Diethylaminoethyl-malondiamide

(a) A soln of compound No. 4 (1·3 g) in MeOH (65 ml) was treated with H_2 and Pd–C (0·2 g) at room temp and atm press. After 1 hr the absorption was complete; the soln was filtered and diethylaminoethyl-malondiamide separated on concentration (0·66 g). m.p. 154–156°. (Found: N. 20·8. $C_9H_{19}N_3O_2$ requires: N. 20·8%.)

(b) Ethyl diethylaminoethylcyanoacetate (3 g) in 95% EtOH (5 ml) was saturated with HCl gas. refluxed for 2 hr and kept overnight at room temp. Some ether and pulverized K_2CO_3 were added and after 6 hr the ether was decanted and evaporated. The oily residue (2·8 g) was treated overnight with NH_4OH (30 ml). with stirring. After evaporation of the solvent. the residue was crystallized from EtOH to give the same compound (1·7 g) that was obtained according to (a).

2-Methyl-4-ethyl-5-aminoisoxazolin-3-one (No. 5)

(a) Methylhydroxylamine. HCl was treated overnight in EtOH and at room temp with 1 equiv EtONa and 0·9 equiv ethyl ethylcyanoacetate. followed by another equiv EtONa. The soln was next heated at 60° for 3 hr and later the solvent was eliminated *in vacuo*. The residue was treated with cold water and crystallized from AcOEt–pet. ether to give compound No. 5 (75% yield).[37]

(b) 4-Ethyl-5-aminoisoxazolin-3-one was treated in MeOH with K_2CO_3 (1·2 equivs) and MeI (1·2 equivs) at reflux temp for 6 hr. The solvent was eliminated and the residue was treated as in (a) to give compound No. 5 in 70% yield

[33] It is known[34] that the Δ (OH) of an intramolecular association band increases on going from 1,2 to 1,4 and 1,5 diols (i.e. from a 5- to an 8- member ring formed in the intramolecular bond): the largest shifts seem to be associated with 7 and 8-member rings.

[34] W. F. Baitinger and P. von R. Schleyer, *14th Meeting of American Chemical Society*. New York, 8–13 September (1963); Abstracts 36 Q.

[35] Only representative procedures are reported.

[36] D. S. Breslow. R. S. Yost. H. G. Walker and C. R. Hauser. *J. Am. Chem. Soc.* **66**. 1921 (1944).

[37] A further crop (about 10%) can be obtained by saturating with CO_2 the water washings.

3-Methoxy-4-ethyl-5-aminoisoxazole

4-Ethyl-5-aminoisoxazolin-3-one (2 g) in CH_2Cl_2 (50 ml) and MeOH (10 ml) was treated with a slight excess of diazomethane. The solvent was eliminated and the residue was crystallized from benzene–pet-ether to give the N-methyl derivative No. 4 (0·5 g). The mother liquors were chromatographed on silica gel: *3-methoxy-4-ethyl-5-aminoisoxazole* was isolated by elution with benzene and distillation at 80° (oil bath) and 0·2 mm Hg (0·8 g). (Found: OCH_3, 21·1. $C_6H_{10}N_2O_2$ requires: OCH_3, 21·8%.)

2-(3-Dimethylaminopropyl)4-ethyl-5-aminoisoxazolin-3-one (No. 8)

4-Ethyl-5-aminoisoxazolin-3-one in MeOH was treated at 70° for 4 hr with 3-dimethylaminopropyl-chloride (1·2 equivs) and K_2CO_3 (2·2 equivs). The soln was filtered and the solvent eliminated *in vacuo*. The residue was dissolved in AcOEt and washed with a saturated soln of Na_2CO_3. Evaporation of the solvent and crystallization from AcOEt–Et_2O afforded compound No. 7 (50% yield).

2-Benzyl-3-amino-4-ethylisoxazolin-5-one (No. 20) *and 3-amino-4-benzyl-4-ethylisoxazolin-5-one* (No. 15)

(a) An aqueous soln of the Na salt of 3-amino-4-ethylisoxazolin-5-one was treated with 1 equiv $AgNO_3$. The precipitated Ag salt (5·8 g), dried at 60°,[38] was suspended in MeCN (60 ml) and treated at reflux with benzyl bromide (1·05 equivs) for 8 hr. The solvent was evaporated *in vacuo* and the residue was taken up in AcOEt. On concentration and addition of ether 3-amino-4-benzyl-4-ethylisoxazolin-5-one (No. 15) separated as white prisms (0·55 g). The residue was chromatographed on silica gel (ether as eluent): the 4-benzyl derivative (No. 15) was eluted first (0·2 g), whereas the following fractions afforded 2-benzyl-3-amino-4-ethylisoxazolin-5-one (No. 20) (1·95 g).

(b) A DMF solution of the sodium salt of No. 1 was treated at 90° for 4 hr with benzyl bromide. The solvent was distilled off *in vacuo* and the residue was chromatographed on silica gel: a first fraction gave by crystallization (AcOEt -Et_2O) compound No. 15 (about 8% yield) and the following fractions afforded compound No 20 (about 70% yield).

(c) A MeOH soln of 3-amino-4-ethylisoxazolin-5-one was treated with benzyl bromide and K_2CO_3 at reflux temp for 3 hr After elimination of the solvent and crystallization from EtOH–ether, compound No. 20 was obtained in 80% yield. The mother liquors were analysed by TLC and same compound No. 15 was found to be present (estimated yield: 4%).

3-Amino-4-methyl-4-butylisoxazolin-5-one (No. 14) *and 2-methyl-3-amino-4-butylisoxazolin-5-one* (No. 18)

The Ag salt (5 g) of 3-amino-4-butylisoxazolin-5-one was treated in MeCN with MeI according to the procedure reported for the preparation of compound 15. The 4-methyl derivative (0·16 g; compound No 14) and the 2-methyl derivative (1·05 g; compound No. 18) were obtained by chromatography on silica gel and crystallization from benzene–ether

3-Amino-4,4-diethylisoxazolin-5-one (No. 16)

Ethyl diethylcyanoacetate (8·5 g) was treated overnight in EtOH at room temp with 1 equiv EtONa and the suspension was next heated at 60° for 4 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in water and extracted with ether. The ether extracts were discarded and the water layer was acidified to pH 4 with H_2SO_4: compound No. 16 slowly separated and was recrystallized from AcOEt (2·2 g).[39]

2-Methyl-3-amino-4-ethylisoxazolin-5-one (No. 17)

(a) Methylhydroxylamine hydrochloride (9·1 g) dissolved in EtOH (60 ml) was treated with one equiv EtONa and ethyl ethylcyanoacetate (14·2 g) was next added. The soln was refluxed for 2 hr, the solvent evaporated *in vacuo* and the residue was treated first with ether and next with hot AcOEt. Compound No. 17 (5 g) separated on cooling from AcOEt soln.

(b) This same compound (80% yield) was obtained by treating 3-amino-4-ethylisoxazolin-5-one (5·12 g) in MeOH (50 ml) with K_2CO_3 (3·2 g) and MeI (6·25 g) at reflux temp for 3 hr and subsequently working up the soln as reported in (a).

2-Diethylaminoethyl-3-amino-4-phenylisoxazolin-5-one (No. 22)

(a) A soln of 3-amino-4-phenylisoxazolin-5-one (4 g) in MeOH (40 ml) was treated at reflux temp for

[38] The salt decomposes explosively when heated at about 150°.

[39] If only 1 equiv of EtONa is used the same compound is formed but in lower yields.

4 hr with diethylaminoethylchloride. HCl[36] (4·9 g) and K_2CO_3 (4·2 g). After elimination of the solvent the residue was crystallized from AcOEt to give No. 22 in 70% yield.

(b) A soln of 3-amino-4-phenylisoxazolin-5-one (1 g) in MeOH (5 ml) was treated with 1,2-dibromoethane (2·9 g) and K_2CO_3 (0·45 g) at room temp for 90 hr. The soln was filtered, the solvent was evaporated *in vacuo* and the residue crystallized from MeOH to give 2-(2-*bromoethyl*) 3-*amino*-4-*phenylisoxazolin*-5-*one* (0·8 g), m.p. 199–200°. (Found: Br, 28·8. $C_{11}H_{11}BrN_2O_2$ requires: Br, 29·1%.)

2-(2-Bromoethyl) 3-amino-4-phenylisoxazolin-5-one (0·8 g) was treated at 80° for 4 h with Et_2NH (15 ml). The solvent was evaporated and the residue was treated with dil HCl and AcOEt: the acid soln was basified with NH_3 and extracted with AcOEt. Evaporation of this AcOEt extract gave a residue (0·5 g) which was crystallized from AcOEt to give a product that was found identical with No. 22 prepared according to (a).

Acknowledgements—We wish to thank Dr. Bruno Camerino, Director of these laboratories, for his interest in this work, Dr. Rosanna Mondelli for the NMR spectra, Dr. Giorgio Diqual for helping in the experimental part and Adriano Alemanni for the microanalysis.