Tetrahedron, 1961, Vol. 12, pp. 51 to 55. Pergamon Press Ltd. Printed in Northern Ireland

THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—II[1]

3-,4- AND 5-AMINO- AND ACETAMIDO-ISOXAZOLES

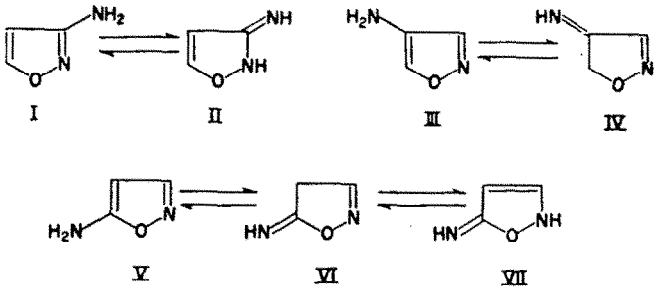
A. J. BOULTON and A. R. KATRITZKY
University Chemical Laboratory, Cambridge

(*Received* 23 *August* 1960)

Abstract—Infra-red and nuclear magnetic resonance spectra show that all types of amino- and acetamido-isoxazoles exist predominantly as such.

Ultra-violet spectroscopy indicates that 3- and 5-amino-isoxazoles are protonated at the ring nitrogen atom, but the 4-amino- analogues on the amino- group. Basicities of these compounds are recorded.

ALL amino-isoxazoles are potentially tautomeric: 3- (I) and 4-amino-compounds (III) are each in equilibrium with one imino-form, II and IV respectively, and 5-amino-compounds (V) are in equilibrium with two imino-forms VI and VII. These possibilities have long been realized—in Beilstein the compounds are classified as imino-derivatives of the corresponding isoxazolones[2]—but little definitive evidence as to the predominating structures is available. For the 5-series, v. Auwers *et al.* argued that chemical evidence favoured the amino-structure (V) rather than the imino- (VI) [imino-forms of type VII were apparently not considered] for the 3-phenyl[3] and 3,4-tetramethylene compounds.[4] Physical methods have not been applied up to now, with the exception of molecular exaltation which did not provide clear-cut evidence.[3,4] Acetamido-isoxazoles could show tautomerism in an exactly analogous way to the amino-compounds.



Following our work on potential 5-hydroxyisoxazoles, we have now investigated typical amino- and acetamido-compounds of each type. Compounds were prepared by known methods (see Tables 1 and 2). Attempted reduction to the amine of 20 g of

[1] Part I: *Tetrahedron* **12**, 41 (1961).
[2] *Beilstein, Hauptwerk* **27**, *inter alia*, pp. 157, 200.
[3] K. v. Auwers and H. Wunderling, *Ber. Dtsch. Chem. Ges.* **67**, 638 (1934).
[4] K. v. Auwers, T. Bahr and E. Frese, *Liebigs Ann.* **441**, 68 (1925).

4-nitro-3,5-dimethylisoxazole with stannous chloride became uncontrollably violent (cf. ref. 5), but amalgamated aluminium foil in moist ether was satisfactory.[6]

Infra-red spectra. An investigation of the spectra of many substituted isoxazoles showed that all bands of appreciable intensity could be assigned to the substituents or to the isoxazole ring.[7] All the amino- and acetamido-isoxazoles presently studied showed the characteristic ring bands[7] and all other bands ($\varepsilon_A > 10$) could be assigned to the amino- (Table 1), acetamido- (Table 2), or other substituents.[7] Spectra of 0·185 M chloroform solutions were measured in 0·108 mm cells and apparent extinction coefficients are recorded.[7]

TABLE 1. INFRA-RED SPECTRA OF AMINO-ISOXAZOLES

	1	2	3	4	5	6	7	lit.
Substituents	N—H stretch		NH_2 scissor and 1st ring mode		νC—N	m.p.	lit. m.p.	ref. 8
3 4 5	asym	sym						
	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A			
NH_2 — Me	3450 35	3370 40	1629 380	1612[a]	1278 85	61–62°	61–62°	11
NH_2 — Et	3480 40	3385 45	1627 420	(–)	1302 10	64–66	64–66	12
NH_2 — Ph[a]	3455 40	3370 50	1629 330	1614[a] 140	1269 20	137–138	139–139·5	12
Me NH_2 Me	3410 20	3345 15	1660 70	1612 40	1272 25	54·5–56	56–57	6
Me — NH_2	3490 60	3395 75	1636 530	1590 65	1333 10	85–86	86	13
Me Me NH_2	3455 45	3360 65	1658 440	1600 105	1240 65 1327 10	121–122·5	125	14
Ph — NH_2	3465 55	3365 85	1635 630	(–)	1335 15 1310 10 1285 10	111–113	110–112	15, 13

[a] additional bands found at 1056 (35), 942 (60).

The amino- compounds all show two bands in the NH stretching region, at 3485–3390 cm^{-1} (20–65) and 3390–3330 cm^{-1} (15–85) (Table 1, cols. 1 and 2). If the 4- and 5-amino- compounds existed in 5H-isoxazol-4-onimine (IV) and 4H-isoxazol-5-onimine forms (VI), respectively, the two bands in the NH region would have to be assigned to hydrogen-bonded and free molecules. This possibility was excluded by showing that the relative intensities of the two bands were unchanged for 4-amino-3,5-dimethyl and 5-amino-3-methyl isoxazole in 0·02 M solutions in 1 mm cells. If the 3- and 5-amino-compounds existed in 2H-isoxazol-3-onimine (II) and -5-onimine forms (VII), respectively, one of the two bands in the νNH region would be due to the hydrogen attached to the cyclic nitrogen and the other to that attached to the exocyclic nitrogen. This possibility was excluded by deuteration experiments. When 3-amino-5-phenyl and 5-amino-3-methyl isoxazole were separately dissolved in deuterium oxide and the compound crystallized out or the solvent evaporated, the hydrogen attached to nitrogen was replaced by deuterium to an extent, under the conditions used, of roughly

[5] R. Justoni, *Gazz. Chim. Ital.* **70**, 802 (1940).
[6] G. T. Morgan and H. Burgess, *J. Chem. Soc.* **119**, 699 (1921).
[7] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* In press.
[8] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* 3674 (1959).
[9] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* 2067, (1959).
[10] A. R. Katritzky and J. M. Lagowski, Review in preparation.
[11] H. Kano and K. Ogata, *Ann. Rep. Shionogi Res. Lab.* **7**, 1 (1957); *Chem. Abstr.* **51**, 17889 (1957).
[12] H. Kano, Personal communication.
[13] P. S. Burns, *J. Prakt. Chem.* **47**, 105 (1893).
[14] H. M. Wuest and M. Hoffer, U.S.Pat. 2,430,094; *Chem. Abstr.* **42**, 1610 (1948).
[15] A. Obrégia, *Liebigs Ann.* **266**, 324 (1891).
[16] H. Kano, *J. Pharm. Soc. Japan* **72**, 1118 (1952).

TABLE 2. INFRA-RED SPECTRA OF ACETAMIDOISOXAZOLES

Substituents 3	4	5	1 νN—H at 0·02 M cm⁻¹	ε_A	2 νN—H free cm⁻¹	ε_A	3 νN—H H-bonded cm⁻¹	ε_A	4 νC=O cm⁻¹	ε_A	5 Amide II cm⁻¹	ε_A	6 CH def. $COCH_3$ cm⁻¹	ε_A	7 νC—N cm⁻¹	ε_A	8 νC—N cm⁻¹	ε_A	m.p.	lit. m.p.	lit. ref.
NHAc	—	Me	3395	60	3395	25	3250* 3215 3140 3085	70 85 65 85	1705	360	1560 1539*	160 140	1381 1371	70 55	—		1280	250	185°	185°	11
Me	NHAc	Me	3410	55	3410	45	3270	45	1691	290	1515	110	1374	70	1325 1280*	15 40	1250	150	108–109	108–109	6
Me	—	NHAc[a]			3400	m	3250* 3210 3140	w w	1715	vs	1548* 1525	s vs	1372	m	—		1262	ms	174–175·5	169	13
Me	Me	NHAc			3390	50	3225 3160*	55	1710	310	1515* 1506	180 200	1376	110	1309	70	1236	150	115–116	114–115	16
Ph	—	NHAc			3380	55	3250* 3200	20 25	1717	185	1546* 1516	160 350	1370	45	—		1266	130	163–164	164	13

[a] saturated solution in chloroform.

80 per cent, as evidenced by infra-red intensities. For 80 per cent exchange the proportion of ND_2:NHD:NH_2 molecules would be 64:32:4. Bands due to ND_2 and NHD molecules could be clearly distinguished:-

Substituent			NHD	ND_2	NHD	ND_2
3	4	5	νN—H cm^{-1}	*asym* νN—D cm^{-1}	νN—D cm^{-1}	*sym* νN—D cm^{-1}
NH_2	—	Ph	3410	2580	2525	2480
Me	—	NH_2	3445	2605	2540	2500 2470

The bands due to the NHD groups absorb at frequencies between those of the NH_2 and ND_2 groups respectively, this proves that the two hydrogen atoms are similarly placed; for the alternative possibilities mentioned above no distinct bands for NHD molecules would be found.

For aromatic amines, the position of each νN—H band rises as the attached ring becomes more electron accepting; the apparent extinction coefficients also increase, that of the symmetrical vibration the more markedly.[8] The mean frequencies indicate that the 3- and 5-positions of the ring accept electrons much more readily than the 4-position. The mean intensities are in the order $4 < 3 < 5$ and the variation is greater for the symmetrical mode; however, the intensities for the 3-amino- compounds are probably lowered by intramolecular hydrogen bonding (cf. 2-amino-pyridine),[8] these results are thus not inconsistent with the frequency variation.

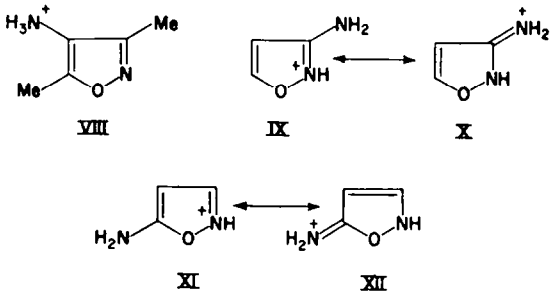
The amino- compounds usually show two bands in the 1600 cm^{-1} region (Table 1, cols. 3 and 4) which are attributed to the NH_2 scissor and a nuclear mode of the isoxazole ring.[7] However, the frequency and intensity of the ring mode in the deuterated compounds show that the two modes in the non-deuterated compounds can become highly mixed.

A weak to medium band in the 1330–1240 cm^{-1} region is presumably the νC—N mode[8] (Table 1, col. 5). The other bands ($\varepsilon_A > 10$) could, with few exceptions given a footnote, be assigned to the ring or other substituent(s).

The NH-stretching region of the spectrum is complex for the acetamido- compounds in 0·2 M solution (Table 2, cols. 2, 3), but examination of 0·02 M solutions (Table 2, col. 1) shows that one band is due to free νNH and the others to intermolecular hydrogen bonded νNH, as is often found.[9] All compounds show the νC=O, Amide II, and other bands associated with the acetamido- group;[9] the overall spectra afford strong evidence that these compounds exist predominantly in the acetamido- forms.

Ultra-violet spectra of neutral amino-isoxazoles and their cations in aqueous solution are recorded in Table 3. The 4-aminoisoxazole cation has a spectrum resembling that of 3,5-dimethylisoxazole (λ_{max} 214 mμ), showing its structure to be VIII; the bathochromic shifts which occur on cation formation by 3- and 5-amino-isoxazoles show that their structures are of the IX–X and XI–XII type respectively.

Basicities (Table 3). 4-Amino-3,5-dimethylisoxazole is a base considerably weaker than aniline ($pK_a = 4{\cdot}58$) showing that the isoxazole ring even at the 4-position is more electron accepting than the phenyl. Amino groups in the 3- or 5-positions



VIII IX X

XI XII

increase the basicity of isoxazoles[1] by ca. 2·5 pK units; for comparison, 2- and 4-amino-groups increase the basicity of pyridine by 1·7 and 4·0 pK units, respectively.

*Nuclear magnetic resonance spectra.** The N.M.R. spectra of 4-amino-3,5-dimethyl- and 5-amino-3,4-dimethyl-isoxazole were examined in aqueous and chloroform solutions. The two methyl groups of the 4-amino- compound showed as sharp absorption bands at chemical shifts (τ values) of 7·84 and 7·91 in water,† and at 7·90

TABLE 3. THE ULTRA-VIOLET SPECTRA AND BASICITIES OF AMINOISOXAZOLES

Substituent at positions			1		2		3		4
			Cyclohexane		Solvent water		2 N H_2SO_4		
3	4	5	λ(mμ)	ε	λ(mμ)	ε	λ(mμ)	ε	pK_a
NH_2	H	Me	—		209	6820	230	8040	0·47 ± 0·02[a]
Me	NH_2	Me	239	3020	242	3760	212	4710	3·8 ± 0·1[b]
Me	H	NH_2	227	4820	239	9210	254	12,200	0·64 ± 0·01[a]
Me	Me	NH_2	233	6380	244	8230	263	13,800	1·16 ± 0·01[a]

[a] Measured by the spectrophotometric method;
[b] by the titration method (estimated standard deviation of a single reading).

and 8·00 in chloroform, and those of the 5-amino- compound at 7·94 and 8·36 in water,† 7·97 and 8·35 in chloroform. The amino- groups gave broad bands in the chloroform solutions, the 4-amino- group at 7·32, the 5-amino- at 5·37 p.p.m. In each case the aminoisoxazole rather than the isoxazolonimine structure IV or VI was shown by the absence of splitting of either of the resonances due to the methyl groups, and by the absence of absorption attributable to a lone proton α to a methyl group.

General conclusions. It appears to be a general feature of tautomerism in heterocyclic compounds that the tendency for amino- compounds to exist as such is considerably greater than that for the hydroxy-analogues.[10] As there is little difference between the stabilities of the various tautomers for 5-hydroxyisoxazoles,[1] it is then not unexpected that 5-aminoisoxazoles exist in the amino-form.

Acknowledgement—We are very grateful to Dr. H. Kano for kindly providing specimens of the 3-aminoisoxazoles.

* These spectra were obtained using a Varian Associates 4300B spectrometer and 12″ electromagnet, at 40 Mc/s, with flux stabilisation and sample spinning. The chemical shifts are quoted in parts per million on the silicon tetramethyl (τ) scale.

† measured using t-butanol (τ = +8·78) as internal standard.