Tetrahedron. Vol 25, pp 747 to 759 Pergamon Press 1969 Printed in Great Britain

MASS SPECTROMETRY OF 5-ALKOXYISOXAZOLES AND ISOXAZOL-5-ONES

T. NISHIWAKI

Department of Chemistry, Faculty of Arts and Sciences, Yamaguchi University, Yamaguchi City, Japan

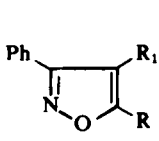
(*Received in Japan* 19 *August* 1968; *Received in the UK for publication* 1 *September* 1968)

Abstract—Mass spectrometry of 5-alkoxyisoxazoles and isoxazol-5-ones were investigated with the aid of high resolution mass spectrometry and deuterium labelling. The spectra of the title compounds generally have an intense (C_3-substituent + CO) ion which is the base peak for the methyl ethers. *A priori* application of known fragmentation patterns to functionally substituted isoxazoles must be exercised with caution. Ions ($M-CO_2R$) apparently associated with the cleavage of an N—O linkage of 5-alkoxyisoxazoles are observed only in the high voltage spectra. Whole features of the mass spectra of 4-arylideneisoxazol-5-ones are also reported. Loss of N—O—CO appears to be general for isoxazol-5-ones including 4-arylidene derivatives.

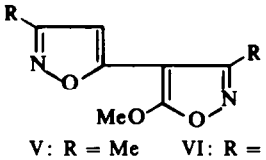
THE mass spectrum of the methyl ether (V) of dimeric 3-methylisoxazol-5-one (VIII),[1] unexpectedly revealed an acetylium ion as the base peak in addition to peaks associated with the cleavage[2a,b] of an N—O linkage. This observation prompted an extension of the work to representative 5-alkoxyisoxazoles (I, IV) and isoxazol-5-ones (IX, X, XI). With the aid of high resolution mass spectrometry and deuterium labelling, several features were disclosed. Unfortunately, ^{18}O-labelled compounds were unavailable leaving some ambiguity as to the origin of the incorporated O atom into ions. Nevertheless, the results are important because of the apparent operation of skeletal rearrangements[3] in the formation of intense peaks including base peak, processes very troublesome for the correct interpretation of computerized element mapping of fragment ions. In addition, the behaviour of 4-arylideneisoxazol-5-ones under electron impact has been given in a preliminary report.[4]

Preparation of labelled compounds. Labelled methyl ethers II and III were obtained by treatment of IX with methanol and sulphuric acid-d_2 or methanol-d_4 and sulphuric acid-d_2. Reaction of ketene dimer with methanol-d_1 yielded methyl γ-monodeuterio-acetoacetate (isotopic purity, ca. 100%), which on condensation with hydroxylamine hydrochloride produced VIII deuteriated on both of the side chains. Treatment of this compound with diazomethane gave VI as well as an N-methylated derivative. VII* was obtained by deuteriomethylation[5] of VIII. 3-Monodeuteriomethylisoxazol-5-one was prepared[6] and condensed with the appropriate aldehyde in the presence of hydrochloric acid to XIV, XVII, and XXII. Benzaldehyde -α-d was synthesized according to Bennett *et al.*[7] and anisaldehyde-α-d resulted from the reduction of anisil (LAD) and cleavage of the deuteriated diol with lead tetracetate. These two labelled aldehydes yielded XIII (isotopic purity, ca. 90%)[4] and XXI (isotopic purity,

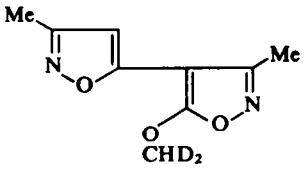
* As it was hoped to obtain a compound unlabelled at an olefinic position, an active hydrogen of VIII was not exchanged prior to deuteriomethylation.



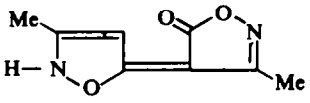
I: R = OMe, R_1 = H
II: R = OMe, R_1 = D
III: R = OCD_3, R_1 = D
IV: R = OEt, R_1 = H



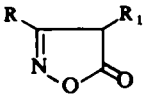
V: R = Me VI: R = CH_2D



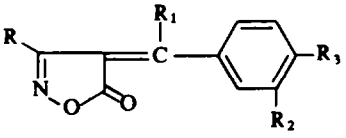
VII



VIII



IX: R = Ph, R_1 = H
X: R = Ph, R_1 = Me
XI: R = Me, R_1 = H



XII: R = Me, R_1 = R_2 = R_3 = H
XIII: R = Me, R_1 = D, R_2 = R_3 = H
XIV: R = CH_2D, R_1 = R_2 = R_3 = H
XV: R = Me, R_1 = Me, R_2 = R_3 = H
XVI: R = Me, R_3 = Me, R_1 = R_2 = H
XVII: R = CH_2D, R_3 = Me, R_1 = R_2 = H
XVIII: R = Me, R_2 = Me, R_1 = R_3 = H
XIX: R = Me, R_3 = Cl, R_1 = R_2 = H
XX: R = Me, R_3 = OMe, R_1 = R_2 = H
XXI: R = Me, R_3= OMe, R_1 = D, R_2 = H
XXII: R = CH_2D, R_3 = OMe, R_1 = R_2 = H
XXIII: R = Ph, R_1 = R_2 = R_3 = H
XXIV: R = Ph, R_1 = D, R_2 = R_3 = H
XXV: R = Ph, R_3 = Me, R_1 = R_2 = H

ca. 100%).* Labelled 3-phenyl-4-benzylideneisoxazol-5-one (XXIV) was obtained by fusing IX with labelled benzaldehyde.[8]

The isotopic purity of most of these labelled compounds had to be assumed by indirect methods[4] or only in a qualitative manner, because the methyl ethers I and V have a small molecular ion (R.I. 2–6%) in their mass spectra whereas the 4-arylideneisoxazol-5-ones have an intense $(M-1)^+$. Approximate calculation revealed that II is ca. 60% pure while III is ca. 80% pure. Although qualitative comparison of the molecular region peaks suggests that both VI and VII do include d_2-species, the content appeared to be $d_1 > d_2 > d_0$ for VI and $d_1 > d_0 \geqq d_2$ for VII. In spite of this they served well for diagnostic purposes.

* An $(M-1)^+$ of XX was small, which made it possible to determine the purity directly from its mass spectrum in the routine manner.

TABLE 1. ACCURATE MASS DETERMINATION DATA

Compound	*m/e*	Found	Formula	Calc.	Compound	*m/e*	Found	Formula	Calc.
I	43	43·018	C_2H_3O	43·018	V	41	41·029	C_2H_3N	41·027
		43·054	C_3H_7	43·055			41·003	C_2HO	41·003
	77	77·039	C_6H_5	77·039		43	43·019	C_2H_3O	43·018
	103	103·045	C_7H_5N	103·042			43·054	C_3H_7	43·055
	105	105·037	C_7H_5O	105·034		54	54·032	C_3H_4N	54·034
	116	116·051	C_8H_6N	116·050		58	58·041	C_3H_6O	58·042
	120	120·057	C_8H_8O	120·058		59	59·012	$C_2H_3O_2$	59·013
	144	144·047	C_9H_6NO	144·045			59·047	C_3H_7O	59·050
	147	147·069	C_9H_9NO	147·069		135	135·054	$C_7H_7N_2O$	135·056
						140	140·036	$C_6H_6NO_3$	140·035
IX	77	77·039	C_6H_5	77·039			140·070	$C_7H_{10}NO_2$	140·071
	103	103·058	C_8H_7	103·055		153	153·046	$C_7H_7NO_3$	153·043
	105	105·037	C_7H_5O	105·034		163	163·050	$C_8H_7N_2O_2$	163·051
		105·061	C_7H_7N	105·058		166	166·075	$C_8H_{10}N_2O_2$	166·074
	106	106·044	C_7H_6O	106·042					
			$^{13}CC_6H_5O$	106·037	XVIII	104	104·063	C_8H_8	104·063
		106·070	$^{13}CC_6H_7N$	106·061		119	119·050	C_8H_7O	119·050
	119	119·035	C_7H_5NO	119·037		126	126·046	$C_{10}H_6$	126·047
						127	127·055	$C_{10}H_7$	127·055
XII	90	90·049	C_7H_6	90·047		128	128·064	$C_{10}H_8$	128·063
	102	102·045	C_8H_6	102·047		129	129·038	C_9H_5O	129·034
	105	105·034	C_7H_5O	105·034			129·067	$C_{10}H_9$	129·070
	126	126·047	$C_{10}H_6$	126·047		143	143·086	$C_{11}H_{11}$	143·086
	127	127·052	$C_{10}H_7$	127·055		160	160·055	$C_{10}H_8O_2$	160·052
	128	128·062	$C_{10}H_8$	128·063					
	129	129·033	C_9H_5O	129·034					
		129·070	$C_{10}H_9$	129·070					
	146	146·035	$C_9H_6O_2$	146·037					

Mass spectra of 5-alkoxyisoxazoles and isoxazol-5-ones. The spectrum of the methyl ether (I) displays an *m/e* 105 (C_7H_5O solely: results of accurate mass determinations are indicated in Table 1) as the most intense peak both at 80 eV (Fig. 1a) and 15 eV (Fig. 1b). In the mono- (II) and tetra- (III) deuteriated compounds this species does not shift showing that hydrogens participating come solely from a phenyl portion and that there is no hydrogen scrambling prior to the collapse of M^+. As further decomposition yields $C_6H_5^+$ (Fig. 1a), it must be a benzoyl ion. A similar situation prevails for the ethyl ether (IV), the *m/e* 105 being observed as the base peak (80 eV; Fig. 2a) or 80% intensity (15 eV; Fig. 2b). For the spectra of 3-phenylisoxazol-5-ones (IX and X) the *m/e* 105 (C_7H_5O 40% and C_7H_7N 60% for IX) again carries a large ion current (Fig. 4 and Table 2). The spectrum of V displays an *m/e* 43 (C_2H_3O 60% and C_3H_7 40%) as the base peak (Fig. 3). One mass shift was observed for the spectrum of VI whereas this species remains at *m/e* 43 for VII and hence we can see that again in this case one of the two C_3-methyls participates in the composition of the base peak. However, the spectrum of XI has so small an *m/e* 43 that a detailed examination was not undertaken.

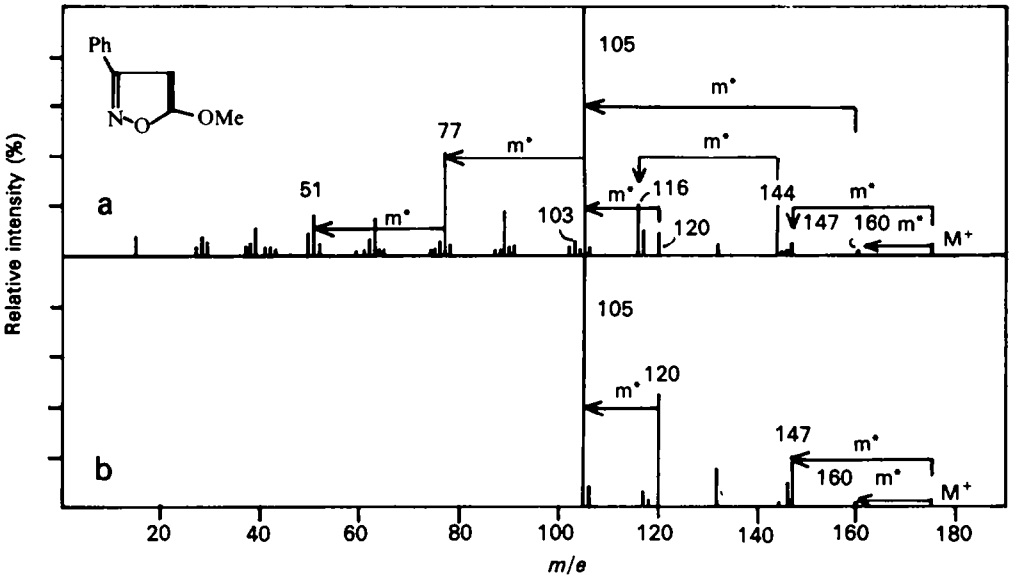
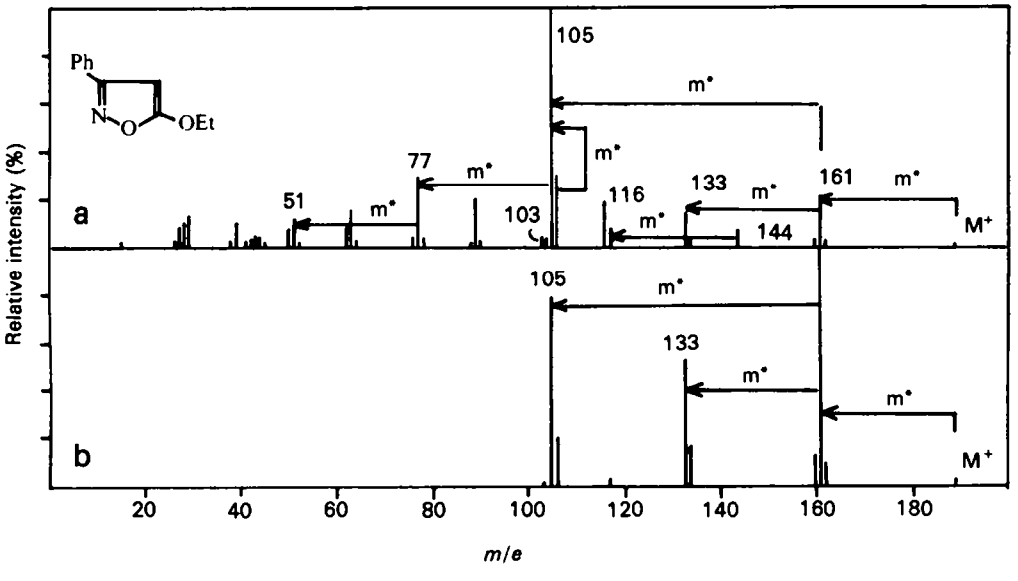


FIG. 1 Mass spectra of I. a— 80 eV. b— 15 eV.



A metastable transition: *m/e* 144 → *m/e* 117 of Fig. 2a should read *m/e* 144 → *m/e* 116.

FIG. 2. Mass spectra of IV. a— 80 eV. b— 15 eV.

TABLE 2. PARTIAL MASS SPECTRA OF X, XI, XV, XVI, XIX, XXIII, AND XXV [a,b,c]

X	*m/e*	103	104	105	106	130	131	(M-44)	132	133	147	(M-28)	175	(M^+)
	RI (%)	30	100	78	64	18	21		15	6	11		15	
XI	*m/e*	41	42	54	55	(M-44)	57	71	(M-28)	72	99	(M^+)		
	RI (%)	100	25	10	3		3	38		2	24			
XV	*m/e*	44	103	104	105	127	128	129	130	131	132	156	157	(M-44)
	RI (%)	100	12	9	20	8	23	9	7	8	3	27	28	
	m/e	158	186	200	201									
	RI (%)	8	8	9	30									
XVI	*m/e*	43	117	119	127	128	129	130	131	132	(M-69)	141	142	143	(M-58)
	RI (%)	8	5	6	12	62	8	3	18	25		14	7	37	
	m/e	144	145	186	200	201	(M^+)							
	RI (%)	6	26	35	17	100								
XIX	*m/e*	43	126	127	128	129	139	140	141	151	152	(M-69)	153	154	163
	RI (%)	94	24	63	98	12	10	4	5	16	25		7	7	51
	m/e	(M-58)	164	165	186	220	221	(M^+)	222	223					
	RI (%)		12	17	15	21	100		18	33					
XXIII	*m/e*	102	103	104	105	106	118	(M-131)	248	249	(M^+)				
	RI (%)	100	42	26	48	7	13		38	76					
XXV	*m/e*	105	119	132	(M-131)	248	262	263	(M^+)						
	RI (%)	43	9	11		30	19	100							

[a] For simplicity, important mass regions necessary to understand the text are cited here and for the same reason reproduction of the spectra of deuteriated compounds were entirely omitted. The full spectra and other unrecorded compounds: 3-methyl-4-isopropylidene-, 3-phenyl-4-*p*-chlorobenzylidene-, and 3-phenyl-4-*p*-bromobenzylideneisoxazol-5-ones are available on request.

[b] Sympton of decomposition in a heated system was noticed for X. In spite of its high purity several small peaks were observed at the region higher than M^+.

[c] Chlorine-containing peaks were not corrected for ^{13}C contents.

Formation of the $C_7H_5O^+$ can be traced to several precursors. This is illustrated by reference to Fig. 1. An *m/e* 120 for I (solely C_8H_8O) shifts to *m/e* 123 for III but stays at *m/e* 120 for II. This species does not appear to be an acetophenone radical ion, because in spite of its possible decomposition[9] into an *m/e* 43 ($MeC{\equiv}O^+$) as well as the *m/e* 105 the *m/e* 43 (C_2H_3O 70% and C_3H_7 30%) is very small (R.I. 3%), which disappears completely in the low voltage spectrum. Additional support for this contention was derived by the close inspection of the spectra of V, VI, and VII, which follow:

(i) There is a metastable ion at *m/e* 32 obviously responsible for the process: *m/e* 58 (C_3H_6O solely) → *m/e* 43.

(ii) Distinct peak shift to *m/e* 59 was seen for VI and to *m/e* 60 for VII.

(iii) The ether methyl does not participate in the *m/e* 43 (if the *m/e* 58 were an acetone radical ion, peak shift for VII is anticipated even if there is a large deuterium discrimination).

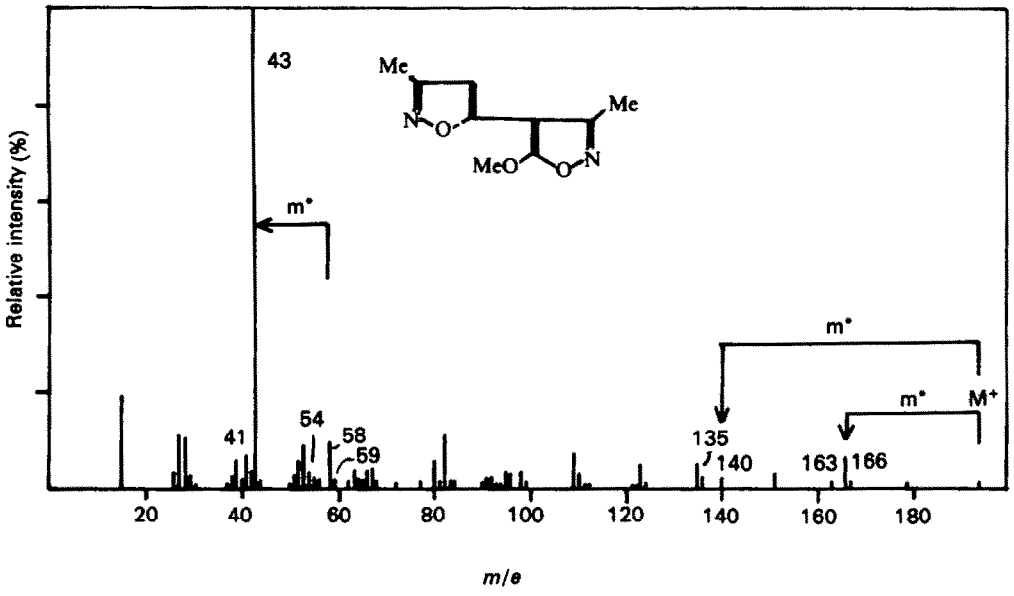


FIG. 3. 80 eV. Mass spectrum of V.

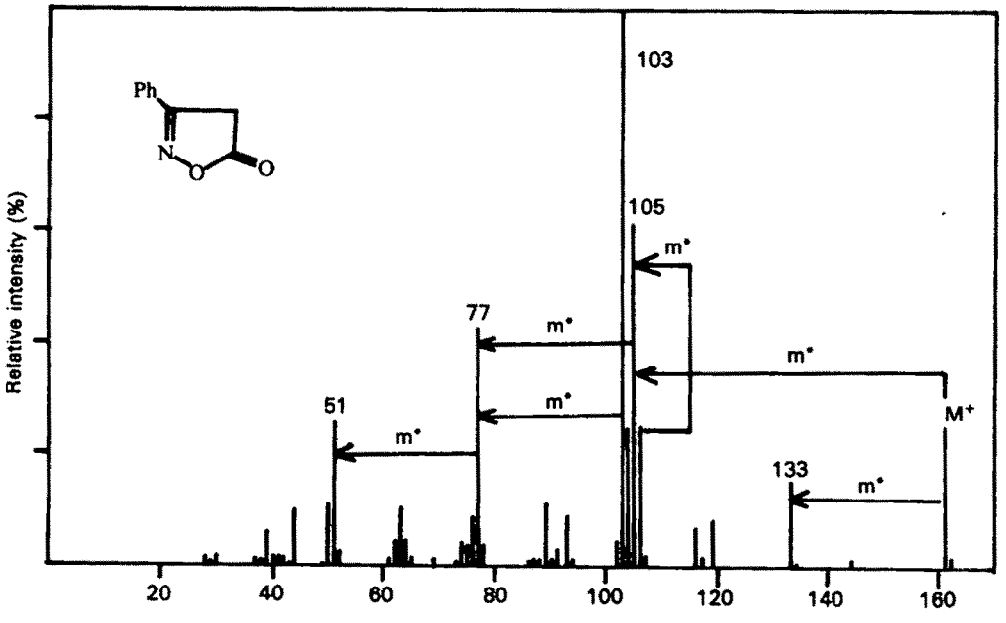
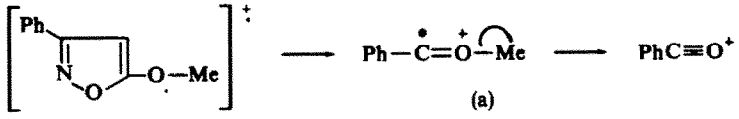


FIG. 4. 80 eV. Mass spectrum of IX.

Based on these observations, the *m/e* 120 of I may be written as (a), from which a Me radical is ejected in forming a benzoyl ion, but further discussion on the genesis of the species (a) is not justified due to the absence of sufficient data.

Another process is $M^+ \rightarrow (M\text{-}Me)^+ \rightarrow C_7H_5O^+$ for I, related pathways being found for IX (and probably X) ($M^+ \rightarrow C_7H_5O^+$) and for IV ($(M\text{-}28)^+ \rightarrow m/e$ 105)). Whatever the true mechanism may be, the (C_3-substituent + CO) ion is easily produced on electron impact of 5-alkoxyisoxazoles and isoxazol-5-ones. This conclusion is further supported by the behaviour of 4-arylideneisoxazol-5-ones.[4]



(a)

At this stage a process: *m/e* 106 → *m/e* 105 observed for IX may be briefly considered. Although an *m/e* 106 is intense in the spectrum (Fig. 4) determined through a heated inlet system, abundance of this species was less than 10% of the *m/e* 105 in the spectrum* obtained through a direct insertion procedure. Result of exact mass measurements of the *m/e* 106 can be roughly accommodated in terms of ^{13}C isotope peaks of the *m/e* 105, but it is considered that the ion C_7H_6O is included in the *m/e* 106 in the latter spectrum, the accurate proportion of which is unknown. Great intensity difference may be due to instrumental or experimental one.

If mass spectrometry is applied to compounds considered to be isoxazolones without realizing the foregoing facts, it may be erroneously concluded that the substances are 5-substituted-3-hydroxyisoxazoles† and therefore great caution is required.

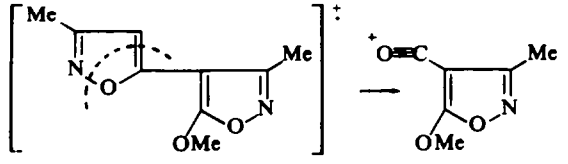
High energy spectra of I, IV, and V have ions presumably triggered by the scission of a vulnerable[12a,b] N—O linkage. This is illustrated by reference to the spectrum of V. An *m/e* 140 ($C_6H_6NO_3$ 50% and $C_7H_{10}NO_2$ 50%) partly shifts to *m/e* 141 for VI whereas shifted peaks are seen up to *m/e* 142 for VII reflecting the retention of the side-chain and methoxy methyls. The ion *m/e* 140 is a daughter ion of M^+ and its complimentary ion (*m/e* 54) has an exact composition of C_3H_4N. An *m/e* 135, explained on the same basis, is solely $C_7H_7N_2O$ and has a complimentary peak at *m/e* 59 ($C_2H_3O_2$ 70% and C_3H_7O 30%). Therefore formation of these four peaks can be ascribed to the cleavage of an N—O linkage (dotted lines). The spectra of VI and VII support the elimination of CO_2Me. But a process: $M^+ \rightarrow (M\text{–}OMe)^+ \rightarrow C_7H_7N_2O^+$ is partly responsible for the *m/e* 135, since an *m/e* 163, though very small in intensity, was found to be solely $C_8H_7N_2O_2$ (M—OMe). The ions $C_6H_6NO_3$ and $C_7H_7N_2O$ may be formulated as (b) and (c), respectively.‡ Another ion resulting from this scission is an *m/e* 41 (C_2H_3N 70% and C_2HO 30%), which needs no further comment because the actonitrile loss is a well documented process for nitrogen heterocycles. This conclusion

* In this insertion procedure the base peak was at *m/e* 51. The *m/e* 103 and 105 ions were 60% intensity, respectively, relative to the base peak.

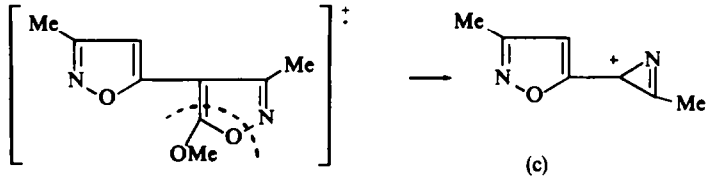
† It has been conclusively shown[10,11] that the reaction product of β-ketoester with hydroxylamine is isoxazol-5-one, but exceptions have been found.[10]

‡ Discussion on the isobaric ions are entirely omitted.

is in keeping with that of Tatematsu *et al.*,[2a,b] but this appears to hold only for the high voltage spectra at least in the 5-alkoxyisoxazoles.



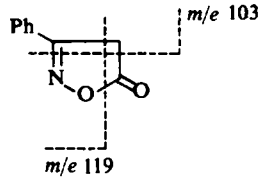
(b)



(c)

The loss of CO_2Me or CO_2Et (one or two processes) from M^+, also found in the 80 eV spectra of I and IV, is supported by appropriate metastable ions and high resolution mass measurement data (*m/e* 144 and *m/e* 116). However, one noteworthy difference can be discerned between Fig. 1a and 1b or Fig. 2a and 2b. The ions associated with the cleavage of an N—O bond (*m/e* 116 and *m/e* 103) are almost entirely absent in the 15 eV spectra. Assumption of less preferred charge localization on a heterocyclic oxygen which may have a higher energy requirement could be one of the possible explanations for this difference.

The remaining features of 5-alkoxyisoxazoles are relatively simple except for an (M—CO) ion in the spectra of I and V, the comment on this being reserved because of the absence of ^{18}O-labelling. The presence of an ($M-C_2H_3O$) for I and V is in accord with a known behaviour of aromatic methyl ethers,[13a,b] while successive eliminations of mass units 28 for IV resemble that of phenetole. Behaviour of IX under electron impact is again simple except for the *m/e*105. Important processes are schematically shown below. It is of interest to note that the base peak is produced by the ejection of an N—O—CO group, which parallels with the behaviour of 4-arylideneisoxazol-5-ones (*vide infra*) and it is possible to conclude that this type of cleavage generally holds for isoxazol-5-ones.



Mass spectra of 4-*arylideneisoxazol*-5-*ones.* Salient features [$(M-69)^+$, $(M-70)^+$, and (C_3-substituent + CO)$^+$] observed in the mass spectra of 4-arylideneisoxazol-5-ones have been reported.[4] For the sake of brevity the 80 eV and 15 eV spectra of

3-methyl-4-benzylideneisoxazol-5-one (XII) and two of its analogues (XVIII and XX) only are cited here (Fig. 5a, b, 6, and 7). The spectra of deuterium labelled compounds XIII, XXI, and XXIV explain the participation of a benzylic hydrogen in the $(M-69)^+$ (3-Me series) or the $(M-131)^+$ (3-ph series), while qualitative comparison with the mass spectra of the compounds labelled differently (XIV, XVII, and XXII) supports the non-participation of the methyl hydrogens in the $(M-69)^+$ ion. It is speculated that a ring expanded ion may intervene in the formation of the $(M-69)^+$ or $(M-131)^+$, in which a ArCH=C=O portion is present, though the ring expansion process must be invoked cautiously. Presence of two O atoms, however, makes the situation complicated and other simple arylidene-substituted carbocycles and/or heterocycles are being studied to obtain more insight into this interesting rearrangement, which was not referred to in a Djerassi's paper.[14] Participation of the methyl hydrogens in the $(M-70)^+$ ion can be concluded, without recourse to the spectra of XIV, XVII, and XXII, from its ion composition and a very complicate mechanism must operate to accomodate the data.

Generally speaking, the high voltage spectra of the 3-methyl series are dominated by intense hydrocarbon ions. The situation will be understood by reference to Table 1, where exact mass measurement data for XII and XVIII are tabulated. Except for XX an *m/e* 128 ($C_{10}H_8$) is very intense. Appropriate metastable ions observed in the spectra of substituted-benzylidene derivatives suggest that the molecular ion is cracked at a dotted line (for example, *m/e* 143 ($C_{11}H_{11}$) of XVIII) followed by the elimination of a substituent leading to the formation of a resonance stabilized aromatic ion, which in

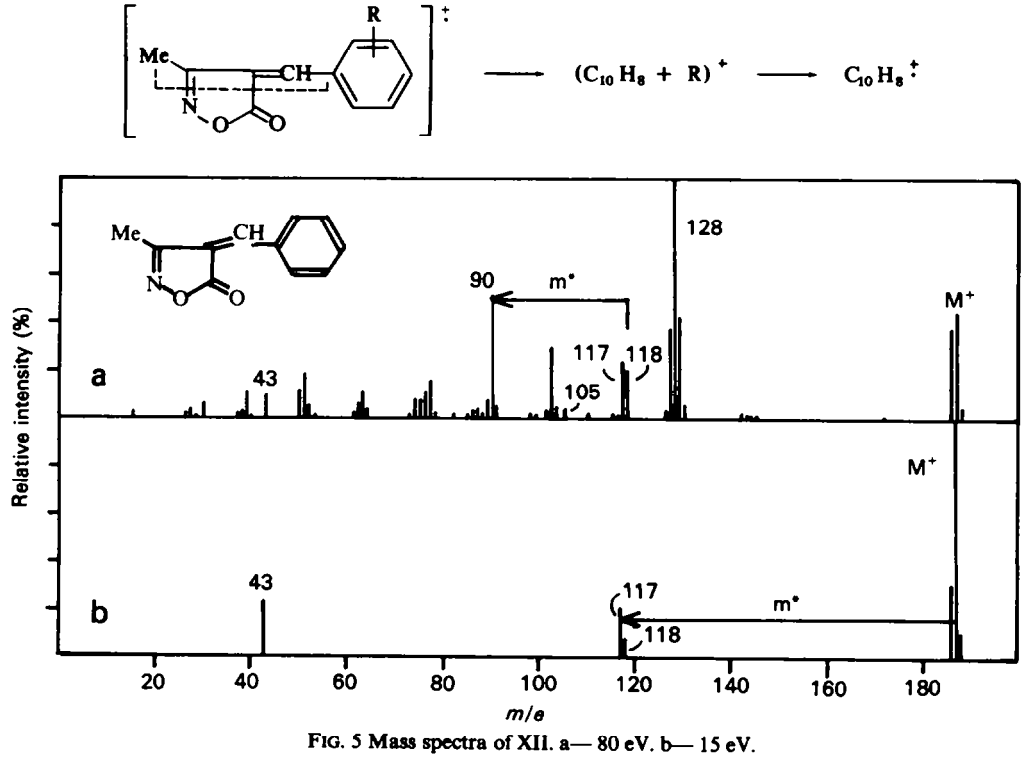


FIG. 5 Mass spectra of XII. a— 80 eV. b— 15 eV.

turn will be a driving force for the elimination of a N—O—CO group. It is, however, considered that this $C_{10}H_8^+$ will not have a specific identity.[15]

The intense (M-1) observed both in the 3-methyl and 3-phenyl series could be due to a bond-forming reaction[16] resulting in an ion such as (d), since deuterium labelling (XIII, XXI, and XXIV) can convincingly reject a benzylidene hydrogen as a leaving one. This view may be further supported by the presence of an intense (M-1) in

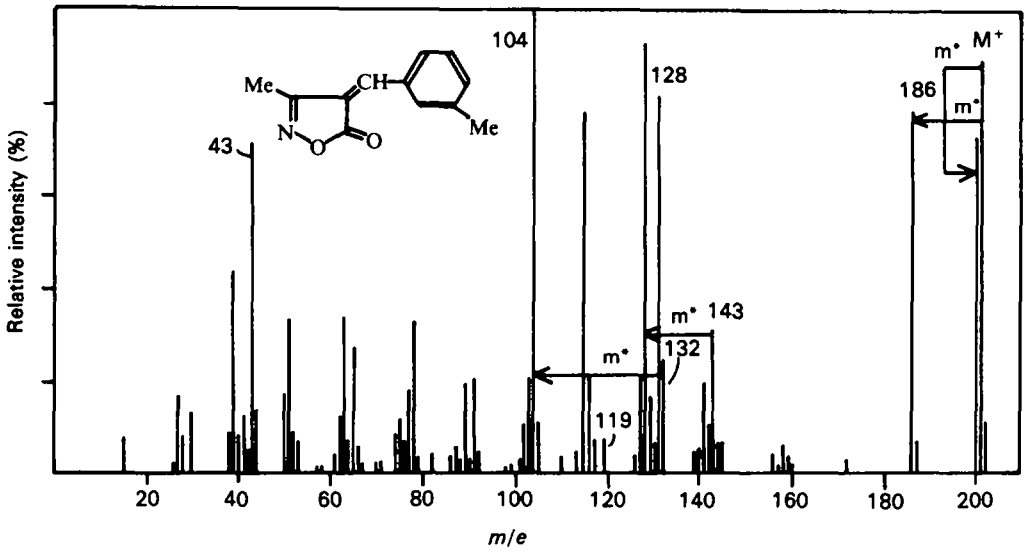


FIG. 6 80 eV spectrum of XVIII.

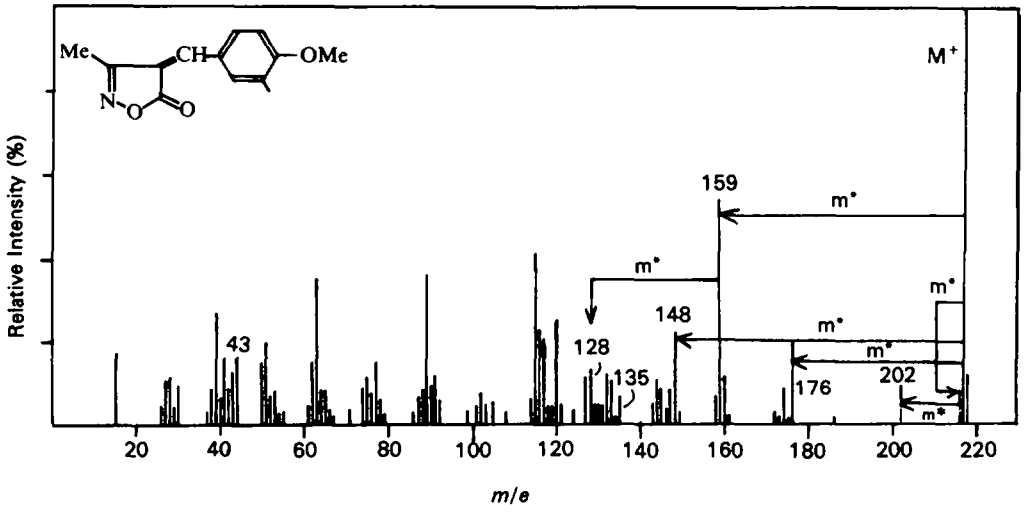
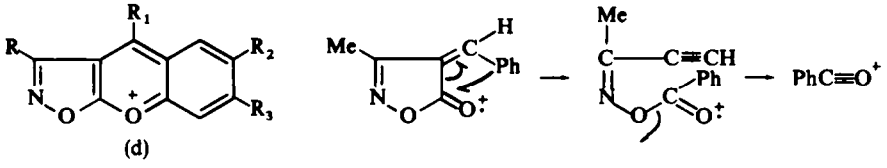


FIG. 7 80 eV spectrum of XX.

para-substituted benzylidene derivatives except for XX and an (M-1) in the spectrum of XV, a leaving hydrogen must originate from a benzene ring. We can exclude the methyl (C_3) hydrogen as the one eliminated because the system N=C—CH_2R is generally reluctant to lose a β-substituent.[17] Non-participation of a vinylic hydrogen is in accord with generally established facts,[18] but it is of interest to record that the spectra of XII and XVIII have ions ascribable to vinylic cleavage, which are C_7H_5O for XII and C_8H_7O for XVIII and probably produced through the following rationalization if the carbonyl oxygen participates or through a skeletal rearrangement[18] of the molecular ion. This process will be responsible for ions at *m/e* 119 (XVI and XXV), *m/e* 139 (and *m/e* 141) (XIX), and *m/e* 135 (XX).



(d)

The third point is that abundances of fragment ions of the 3-methyl series are seriously influenced by the kind and/or position of a substituent on the benzene ring, although overall patterns resemble each other. For example, the *m/e* 128 and its satellites are relatively small for XX compared with other analogues, whereas an (M-41) of XX is much more intense than that of XII and XVIII, for which the leaving group is established as C_2H_3N (Table 1). Further study must be undertaken before this problem can be solved definitely.

EXPERIMENTAL

All of the low resolution mass spectra were obtained through a Hitachi RMU 6D mass spectrometer equipped with all glass inlet system with the following condition: ionization voltage, 80 and/or 15 eV; total ion currents, 80 μA; ion source temp, 200°; inlet system, 200° or 250°. Exact mass measurements were carried out through a CEC model 110-B type spectrometer on a photographic plate. Sample was introduced directly into an ion source (temp, 80°) and 70 eV of ionization energy was applied. Most of the exact mass measurements data were automatically recorded with a microphotometer and comparator and processed by a computer. If any doubt exists, measurements and calculations were repeated by a routine procedure. The spectrum of IX by a direct insertion procedure was obtained through a CEC model 110-B type spectrometer. Deuterium labelled reagents were purchased from Chiba Products, Japan. M.ps were taken in a capillary tube but uncorrected. Petroleum ether had b.p. 30–60°. NMR spectra were run with a Nihon-Denshi type spectrometer.

Preparation of unlabelled compounds. Compounds IX and X as well as the ethers I and IV[11] and compound XI[6,19] were obtained as reported. Transformation of XI into the dimer VIII has been well documented.[6,20]

3-Methyl-4-α-phenylethylideneisoxazol-5-one (XV). The compound XI (3·0 g) and acetophenone (3·6 g) were left in conc HCl (10 ml) for 7 days at room temp, during which time a yellow soln turned dark brown and separated into two phases. The mixture was extracted with ether, the extracts were dried (Na_2SO_4) and evaporated to give an oil, from which any low boiling material was removed *in vacuo*. A brown sticky residue deposited crystals on standing, which were filtered off, washed with a small amount of cold EtOH, and dried on a porous plate. Recrystallizations from n-heptane and then from EtOH (charcoal) yielded light yellow plates, 0·20 g, m.p. 74·5–76°. (Found: C, 71·40; H, 5·38; N, 6·94. $C_{12}H_{11}NO_2$ requires: C, 71·62; H, 5·51; N, 6·96%); NMR spectrum ($CDCl_3$, 60 Mc) showed three peaks at τ 8·41 (s) (=CMe), 7·17 (s) (N=C—Me), and 2·57 (m) (phenyl). This compound gradually turned dark brown and decomposed after about one month.

3-Methyl-4-p-methylbenzylideneisoxazol-5-one (XVI). The compound XI (0·5 g) and *p*-tolualdehyde

(0·6 g) were heated in EtOH (5 ml) and HCl (0·3 ml) for 5 min. The ppt (0·3 g) recrystallized from EtOH as yellow needles, m.p. 129–130°. (Found: C, 71·40; H, 5·38; N, 6·94. $C_{12}H_{11}NO_2$ requires: C, 71·62; H, 5·51; N, 6·96%).

By a similar procedure *3-methyl-4p-methoxybenzylideneisoxazol-5-one* (XX) was obtained as yellow needles (EtOH), m.p. 173–174°. (Found: C, 66·14; H, 5·00; N, 6·00. $C_{12}H_{11}NO_3$ requires: C, 66·35; H, 5·10; N, 6·45%). One or two hr heating was necessary for *3-methyl-4m-methylbenzylideneisoxazol-5-one* (XVIII; light yellow needles (CCl_4–pet ether, 1:1), m.p. 110–112°). (Found: N, 7·04. $C_{12}H_{11}NO_2$ requires: N, 6·96%) and (XIX; yellow rods (benzene–pet. ether, 1:2), m.p. 125–126·5°). (Found: N, 6·13. $C_{11}H_8ClNO_2$ requires: N, 6·32%).

3-Phenyl-4p-methylbenzylideneisoxazol-5-one (XXV). This compound was prepared by fusing IX (0·16 g) and *p*-tolualdehyde (0·12 g) for 5 min, m.p. 177° from EtOH. (Found: C, 77·43; H, 4·91; N, 5·17. $C_{17}H_{13}NO_2$ requires: C, 77·55; H, 4·98; N, 5·32%).

Preparation of labelled compounds

Compound III. Compound IX (0·42 g), CD_3OD (2 ml), and D_2SO_4 (3·0 g) were heated on a boiling water bath for 30 min, the resulting soln was poured into water and adjusted to pH 6 with NaOH aq. The insoluble material was collected and recrystallized from pet. ether, m.p. 74–76°, 20 mg.

Compound II. The above procedure was repeated with MeOH and D_2SO_4.

Compound VI. To a mixture of hot MeOD (10 ml) and anhyd NaOAc (0·2 g) ketene dimer (27·4 g) was added during 1 hr, the mixture being occasionally heated in order to maintain the temp at 60–80° during the addition. After addition, the mixture was maintained at the same temp for 30 min and immediately distilled using a Vigreaux column (20 cm) to give methyl monodeuteriated acetoacetate (12·9 g), b.p. 42–44°/12 mmHg. Freshly cut Na (0·8 g) was added in small pieces into D_2O (10 ml). Hydroxylamine hydrochloride (1·9 g) and the above acetoacetate (2·3 g) were added in that order to the resulting NaOD soln, and the mixture was stirred for 2 hr and left overnight. Acidification with HCl afforded a ppt, which was twice recrystallized from water, m.p. 165–167° (dec), 0·4 g. This was suspended in ether (10 ml) and treated with ethereal diazomethane. The residue was boiled with pet ether (10 ml) and the supernatant liquid decanted off. This process was repeated twice more. The crystals (90 mg) which separated on cooling the decanted soln was purified from pet. ether as colourless rods, m.p. 73–74°. Unlabelled compound prepared in a similar way had m.p. 73–74° and have been correctly analysed as $C_9H_{10}N_2O_3$; NMR spectrum ($CDCl_3$, 60 Mc) of the unlabelled compound had four peaks at τ 7·52 (s), 7·68 (s) (N=CMe), 5·75 (OMe), and 3·85 (=CH). Its physical constant and spectral pattern were in accord with those of Caramella *et al.*[21] Pet. ether insoluble material consisted of unreacted VIII and an N-methyl compound.

Compound VII. Dry THF (20 ml) and D_2O (4·5 ml) were added to an ethereal soln (30 ml) of diazomethane prepared from *p*-tolylsulfonylmethylnitrosoamide (5·0 g). To this soln a mixture of propionic acid (0·2 g) in THF (10 ml) was added during 10 min. The resulting soln was added to a suspension of VIII (0·8 g) in ether (10 ml) and treated as above. The ppt had m.p. 74–75° after purification from pet. ether, 44 mg.

Benzaldehyde-α-d. This was prepared as reported.[7] Exchange was performed in a sealed tube.

Anisaldehyde-α-d. Anisil (5·6 g) was reduced with LAD (0·5 g) in hot ether. Hydrolysis with potassium sodium tartrate afforded a solid, which was extracted with hot $CHCl_3$ (50 ml × 3). Evaporation of the solvent and two recrystallizations from EtOAc afforded labelled dihydroanisoin, 1·3 g, m.p. 171°. The unlabelled compound had m.p. 168–170°.[22] To a stirred soln of dihydroanisoin (1·3 g) in benzene (30 ml) $Pb(OAc)_4$ (2·5 g) was added in portions. After stirring for 1 hr at room temp the solid was filtered off and the solvent evaporated. Purification through the bisulfite adduct gave the labelled aldehyde (0·5 g).

Compounds XIII, XXI, and XXIV were prepared using these labelled aldehydes according to the foregoing methods and had m.ps 143–144°, 175–175·5°, and 189–190°, respectively. Unlabelled XII was prepared (i) according to Schiff *et al.*[23] or (ii) by the condensation of XI with benzaldehyde, m.p. 143–144°, recorded m.p. 141°.[23] Unlabelled XXIII had m.p. 191°.[8] It is noted that under the Schiff's procedure the acid can be replaced with piperidine in alcohol.

3-Monodeuteriomethylisoxazol-5-one. To a cold soln of hydroxylamine hydrochloride (2·5 g) in D_2O (4 ml) K_2CO_3 (2·5 g) in D_2O (5 ml) was added. To this soln ketene dimer (3·0 g) was added during 10 min with ice-cooling and after 30 min the mixture was stirred at room temp for 3 hr. Extraction of the mixture with $CHCl_3$ and distillation of the dried ($CaCl_2$) extracts afforded the compound, b.p. 86–87°/3 mmHg, 1·2 g.

Compounds XIV, XVII, and XXII were obtained from this labelled isoxazol-5-one and had m.ps 143–144°, 129°, and 174°, respectively.

Acknowledgement—I sincerely thank Mr. Nobuhide Wasada, The Government Institute of Technology (Tokyo), for the computer-aided high resolution mass spectrometry.

REFERENCES

[1] J. J. Donleavy and E. E. Gilbert, *J. Am. Chem. Soc.* **59**, 1072 (1937).
[2] [a] M. Ohashi, H. Kamachi, H. Kakisawa, A. Tatematsu, H. Yoshizumi and H. Nakata, *Tetrahedron Letters* 379 (1968);
[b] H. Nakata, H. Sakurai, H. Yoshizumi and A. Tatematsu, *Org. Mass Spectrometry* **1**, 199 (1968).
[3] P. Brown and C. Djerassi, *Angew. Chem.* **79**, 481 (1967).
[4] T. Nishiwaki, *Tetrahedron Letters* 4355 (1968).
[5] K. van der Merwe, P. S. Steyn and S. H. Eggers, *Ibid.* 3923 (1964).
[6] M. Fujimoto and M. Sakai, *Chem. and Pharm. Bull.* **13**, 248 (1965).
[7] D. J. Bennett, G. W. Kirby and V. A. Moss, *Chem. Commun.* 218 (1967).
[8] M. A. Wahl and A. Meyer, *Bull. Soc. Chim. Fr* (4), **3**, 951 (1908).
[9] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass spectrometry of organic compounds* p. 162. Holden-Day, San Francisco (1967).
[10] A. R. Katritzky and S. Oksne, *Proc. Chem. Soc.* 387 (1961).
[11] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).
[12] [a] M. K. Kochetkov and S. D. Sokolov, *Advances in heterocyclic chemistry* **2**, 365 (1963);
[b] N. A. LeBel, T. A. Lajiness and D. B. Ledlie, *J. Am. Chem. Soc.* **89**, 3076 (1967).
[13] [a] C. S. Barnes, D. J. Collins, J. J. Hobbs, P. I. Mortimer and W. H. F. Sasse, *Austral. J. Chem.* **20**, 699 (1967);
[b] F. G. Holliman, R. A. W. Johnstone and B. J. Millard, *J. Chem. Soc.* C, 2351 (1967).
[14] R. L. N. Harris, F. Komitsky, Jr., and C. Djerassi, *J. Am. Chem. Soc.* **89**, 4775 (1967).
[15] R. J. Van Brunt and M. E. Wacks, *J. Chem. Phys.* **41**, 3195 (1964).
[16] J. Ronayne, D. H. Williams and J. H. Bowie, *J. Am. Chem. Soc.* **88**, 4980 (1966).
[17] K. Biemann, *Mass Spectrometry. Organic chemical applications* p. 134. McGraw-Hill, New York (1962).
[18] p. 18 of Ref. 9.
[19] A. R. Katritzky, S. Oksne and A. J. Boulton, *Tetrahedron* **18**, 777 (1962).
[20] G. Lo Vecchio, G. Lamonica and G. Cum, *Biochim. Appl.* 10, 131 (1963); *Chem. Abstr.* **60**, 1725 (1964).
[21] P. Caramellia and P. Grünanger, *Chim. Ind. Milan* **49**, 1335 (1967).
[22] J. S. Buck and S. S. Jenkins, *J. Am. Chem. Soc.* **51**, 2163 (1929).
[23] R. Schiff and M. Betti, *Ber. Dtsch. Chem. Ges.* **30**, 1337 (1897).