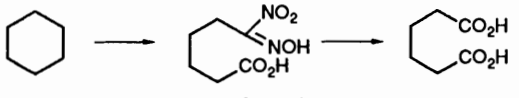
Mechanism of Reaction of Isomeric Nitrolic Acids to Nitrile Oxides in Aqueous Solution

Carmel Egan, Maurice Clery, Anthony F. Hegarty* and Alan J. Welch
Chemistry Department, University College Dublin, Belfield, Dublin 4, Ireland and Chemistry Department, University of Edinburgh, Edinburgh EH9 3JJ, Scotland, UK

Both *E* and *Z* isomers of acetonitrolic acids **15** and **16** can be prepared when the OH group is protected by acetylation. Photoisomerization of the *E*-isomer resulted in quantitative conversion into the pure *Z*-isomer **16**. Hydrolysis of the *E*-isomer **15** produced the parent nitrolic acid **14** which undergoes loss of NO_2^- from the conjugate base at high pH. This reaction is however relatively slow suggesting base solubility and acidic reprecipitation as a method of purification of *E*-nitrolic acids. Deprotection of (*Z*)-*O*-acetylacetonitrolic acid by HO^- gives a highly reactive *Z*-nitrolic acid **17** which undergoes loss of NO_2^- at a rate which precludes its detection; however the subsequent reactions of acetonitrile oxide (CH_3CNO) formed were monitored. Rapid loss of NO_2^- therefore occurs when there is assistance from an antiperiplanar lone pair on the imino nitrogen of the oximate anion. Arylnitrolic acids were also examined; these were in the *E* configuration **26** and therefore underwent slow loss of NO_2^-. Since NMR and IR data are unreliable for the assignment of configuration of nitrolic acids (relative to other oximes) a single crystal diffraction study was carried out on *E*-acetonitrolic acid **14**. The large difference in reactivity observed for the *E*- and *Z*-nitrolic acids now permits strong supporting evidence for structural assignments.

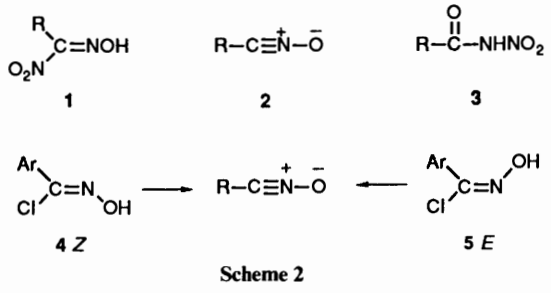
Nitrolic acids (α-nitro oximes) are intermediates in the oxidation of cyclohexane by nitric acid and related oxidizing agents,[1] *en route* to adipic acids (Scheme 1). Similar intermediate nitrolic



Scheme 1

acids have been isolated on treatment of cyclohexanol with nitric acid.[2] Recent work has also been concerned with the formation (and toxicology) of nitrolic acids on the reaction of sorbic acid (and other foodstuffs) with sodium nitrite.[3] The question then arises as to the stability of the nitrolic acid functional group (**1**) in aqueous solution and whether the final step in the conversion is rate determining for the overall reaction.

There have been a number of reports on the reactivity of nitrolic acids **1** and on a reported rearrangement to *N*-nitroamides **3**.[4,5] In addition nitrolic acids have been used as precursors of nitrile oxides **2** in cycloaddition reactions. All nitrolic acids and in particular the aromatic analogues appear to have a low intrinsic stability and undergo a number of reactions, even when stored as solids at low temperature.

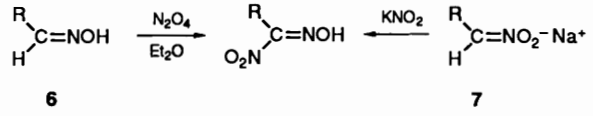


Scheme 2

We have previously demonstrated[6,7] the critical dependence of the stability of hydroximoyl chlorides on oxime configuration; the loss of Cl^- from the *Z*-isomer **4** occurs *ca.* 10^7 times more rapidly than from the *E*-isomer **5**. This has been attributed to the stereoelectronic effect of the antiperiplanar arrangement of the lone pair on the adjacent imino nitrogen and the leaving group in the reactive isomer **4**. The effect of configuration on nitrolic acid reactivity has not been considered in detail before although a similar potential exists. We now report the crystal structure of (*E*)-acetonitrolic acid (which establishes unequivocally the configuration of both series of nitrolic acids) and on the reactivity of isomeric aromatic and aliphatic nitrolic acids.

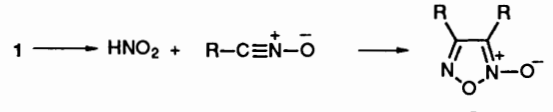
Results and Discussion

Synthesis of Isomeric Nitrolic Acids.—Addition of dinitrogen tetraoxide to oximes **6**,[8–10] nitronic acids[9–11] or nitronate salts,[10,12] leads to nitrolic acids or pseudonitroles. The action of dinitrogen tetraoxide upon aldehyde oximes has been investigated in detail for benzaldehyde oxime,[13] acetaldehyde oxime and propionaldehyde oxime.[14] The reaction of nitrous acid with nitronic acid and salts yields pseudonitroles; the latter derived from primary nitronic acids isomerize readily to nitrolic acids.[15–18] This reaction was first discovered by Meyer[17,18] who prepared acetonitrolic acid by addition of dilute acid to a mixture of nitroalkane anion **7** and potassium nitrite.

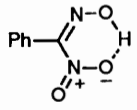


Scheme 3

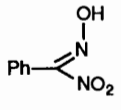
Nitrolic acids[12] are colourless or pale yellow solids which decompose on warming, prolonged storage or treatment with base, eliminating the elements of nitrous acid. The nitrile oxide that results rapidly forms trimers or dimerizes to form furoxanes **8**.



The available data indicate that the stability of nitrolic acids is increased when R is electron donating *e.g.* methyl or ethyl and is decreased when R is electron withdrawing, *e.g.* phenyl or acetyl. There are reports in the literature of isomeric nitrolic acids.[10,19] Several benzonitrolic acids have been obtained in two distinct forms which are different from the tautomeric α-nitro-α-nitrosotoluene forms or their dimers. The IR spectra are grossly similar but show such differences as to suggest that the forms are possibly geometric isomers. Since the *Z*-form **9** should favour the formation of intramolecular hydrogen bonds



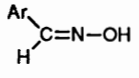
9



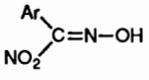
10

between the hydrogen of the hydroxy group and the oxygen of the nitro group, structural assignments were made previously on this basis.

The arylnitrolic acids **12** were synthesized by the action of dinitrogen tetraoxide on the parent aldehyde oxime **11**. Nitrogen dioxide gas (brown) was condensed to a liquid (green) at 0 °C and added to an ether solution of the appropriate



11



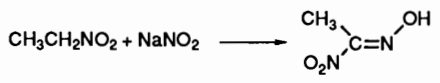
12

Ar
a; Ph
b; *p*-$NO_2C_6H_4$
c; *o*-$NO_2C_6H_4$
d; *m*-$NO_2C_6H_4$
e; *p*-ClC_6H_4

aldehyde oxime. Except for *o*-nitrobenzonitrolic acid **12c** all arylnitrolic acids were obtained as an isomeric mixture; this was easily deduced from the NMR spectra in the case of *p*-nitrobenzonitrolic acid **12b** and *p*-chlorobenzonitrolic acid **12e**. A single isomeric form could be isolated by dissolving the mixture in ice-cold 10% aqueous potassium hydroxide when decomposition products of one isomer immediately precipitated. On dropwise addition of 5% hydrochloric acid to the filtered aqueous potassium hydroxide the *E*-isomer separated from solution. *p*-Nitrobenzonitrolic acid **12b** was unstable to acid. However after several weeks, when the original mixture, was stored at −15 °C, it gave an NMR spectrum which showed a clear AA′BB′ pattern indicative of a single isomeric form of this compound.

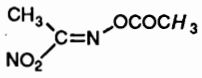
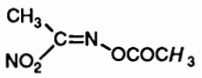
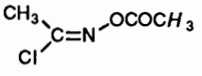
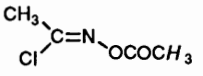
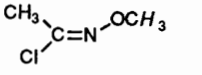
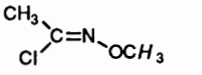
The acetonitrolic acids had previously not been obtained in geometrically isomeric forms. However two series of salts have been observed, one red and one colourless, attributed to geometric isomerism. The red salts were converted into the colourless ones on heating or exposure to light. Only the red salts regenerate the original nitrolic acid on acidification, but both give the same ultimate hydrolysis products. Thus although *E*/*Z* isomerization is possible in the nitrolic acid series, structural assignments have not been unequivocally made.

Acetonitrolic acid **14** was synthesized by reaction of nitroethane **13** with sodium nitrite in 20% aqueous sodium hydroxide at 0 °C. Subsequent acidification and basification of the reaction mixture gave the desired product. This was



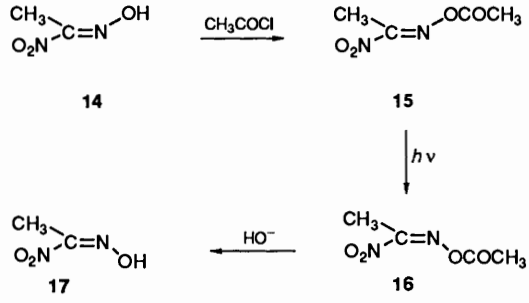
13 **14** (*E*)

Table 1 NMR spectra of *O*-acetylacetonitrolic acid and related oxime derives

E-Isomers	δ	*Z*-Isomers	δ
	2.71		2.63
	2.12		2.30
	3.92		4.06

obtained as a single isomer and attempts to photoisomerize it directly were unsuccessful.

In the case of substituted hydroximoyl chlorides **4** we previously[7] found that it was possible to photoisomerize the oximes only when the OH group was replaced by an alkyl or acyl group; presumably this blocks rapid prototropic isomerization back to the starting oxime. In this work we have used the acetyl group as the most suitable protecting group to allow photoisomerization and separation of the isomeric mixture by preparative TLC.



14 **15** **16** **17**

The acetyl derivative **15** of acetonitrolic acid **14** was synthesized by the reaction of this nitrolic acid with acetyl chloride in dry benzene. The ester **15** was photoisomerized by UV photolysis for 24 h giving 100% conversion into the *Z*-isomer **16**. Such a high conversion on irradiation is quite unusual since other oxime derivatives typically give *E*/*Z* mixtures in the range 1:1 to 3:1. Subsequent removal of the protecting group gave a route to *E*- and *Z*-acetonitrolic acids **14** and **17**. Of the arylnitrolic acids **12**, only the unsubstituted derivative **12a** was successfully acylated (and was sufficiently stable to permit isolation under the reaction conditions used).

Assignment of Structure.—The ^1H NMR spectra of the ester derivatives **15** and **16** were quite distinctive with noticeable shifts in both the acetyl and methyl group hydrogens (see Table 1 for *O*-acetyl signals, and Fig. 1). NMR is widely used in the assignment of oxime configurations and initially we incorrectly assigned the structures of **15** and **16** on this basis. Thus, the acetyl protons were previously reported to be further upfield in the *E*- than in the *Z*-isomer (see Table 1) of aromatic *O*-acetylhydroxyimidoyl chlorides.[7] A similar difference was noted by Johnson[20] (when allowance is made for the fact that the assignments made in this paper were later reversed). If this correlation also holds in the nitrolic acid series then the isomer with the acetyl group resonance at δ 2.71 would be assigned *Z* and that with δ 2.63 would be *E*. However we were not

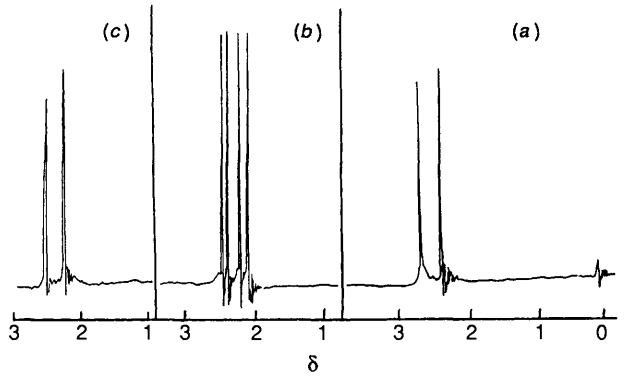


Fig. 1 ^{1}H NMR spectra of (*a*) *O*-acetylnitrolic acid **15** (in $CDCl_3$) (*b*) after 12 h irradiation (1:1 mixture of **15** and **16**) and (*c*) after 24 h irradiation (100% conversion to **16**)

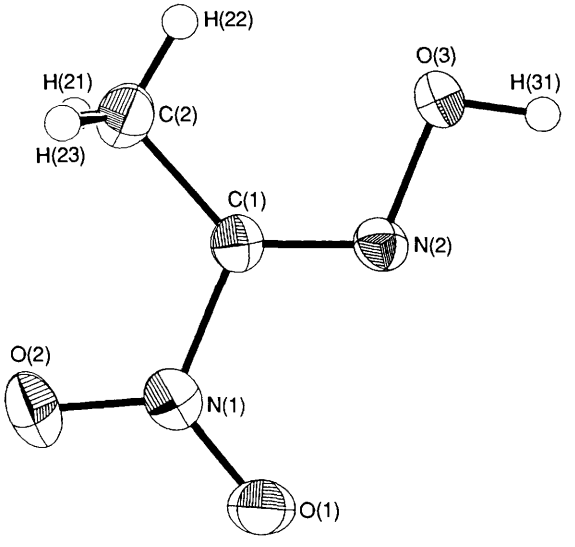


Fig. 2 ORTEP plot of (*E*)-acetonitrolic acid **14**. AU atoms drawn with 30% probability ellipsoids, except H atoms which have an artificial radius of 0.1 Å for clarity.

Table 2 Internuclear distances/Å and interbond angles/° in (*E*)-acetonitrolic acid **14**

Bond	Length/Å	Bond	Length/Å
O(1)-N(1)	1.224(4)	N(2)-O(3)	1.382(4)
N(1)-O(2)	1.214(4)	C(2)-H(21)	0.99(4)
N(1)-C(1)	1.482(4)	C(2)-H(22)	0.95(4)
C(1)-N(2)	1.263(4)	C(2)-H(23)	0.84(5)
C(1)-C(2)	1.480(5)	O(3)-H(31)	0.90(4)

Bond	Angle/°	Bond	Angle/°
O(1)-N(1)-O(2)	124.5(3)	C(1)-C(2)-H(21)	110.4(24)
O(1)-N(1)-C(1)	118.9(3)	C(1)-C(2)-H(22)	109.3(25)
O(2)-N(1)-C(1)	116.5(3)	C(1)-C(2)-H(23)	109.0(33)
N(1)-C(1)-N(2)	112.1(3)	H(21)-C(2)-H(22)	103.8(35)
N(1)-C(1)-C(2)	117.0(3)	H(21)-C(2)-H(23)	113.2(41)
N(2)-C(1)-C(2)	130.9(3)	H(22)-C(2)-H(23)	110.9(41)
C(1)-N(2)-O(3)	111.8(3)	N(2)-O(3)-H(31)	103.4(28)

convinced of this assignment (mainly on the basis of the kinetic analysis, see below) and therefore carried out an X-ray crystallographic study on the more stable isomer (m.p. 84–85 °C). The data were collected at 185 K since a preliminary attempt at 298 K was unsuccessful with visible decomposition of the nitrolic acid occurring.

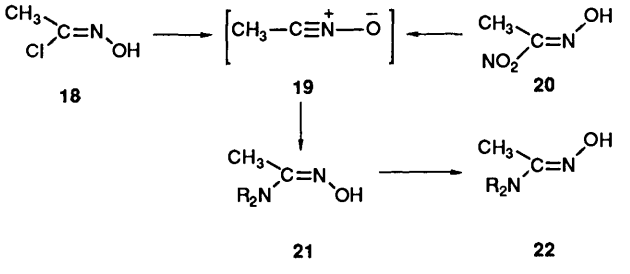
The structure obtained (Fig. 2) clearly shows an *E* configuration for **14** and on the assumption that the configuration does not change on acetylation (which is supported by kinetic studies as shown below) this assignment is used throughout to establish the configurations of all the nitrolic acids.

In the solid state individual molecules of **14** are linked *via* strong hydrogen bonding (and there is evidence that this persists in solution, see below) between H(31) and O(1′)-[H(31) at *x*,*y*,*z*; O(1′) is O(1) at 0.5 + *x*, 0.5 − *y*, −1 − *z*], with H(31)···O(1′) 2.29(4) Å, O(3)–H(31)···O(1′) 127(4)° and H(31)···O(1′)–N(1′) 109.7(11)°. Intramolecular bond distances and bond angles are listed in Table 2. The $C_2N_2O_3$ skeleton of the molecule is planar (esd 0.018 Å) and molecular parameters within it are in good agreement with those in related molecules.[21,22]

The failure of the NMR correlation (see Table 1) is probably attributed to the key role played by a *C*-aryl group in determining the position of the OCH_3 and $OCOCH_3$ resonances in the *E*- and *Z*-isomers; the CH_3 groups are shielded when *cis* to the aryl group (which of necessity is rotated out of the C–N–O plane in the *E*-isomer).

The *E*-acetonitrolic acid **14** shows a broad OH absorption in the range 3280–3380 cm^{-1}; such absorptions have previously[23] been assigned to intramolecular H-bonding between adjacent NO_2 and OH groups in nitrolic acids. However since the OH and NO_2 groups are clearly *trans* to one another, this band broadening in **14** must arise from another cause *e.g.* intermolecular H-bonding (as observed in the X-ray structure). In view of these findings NMR and IR assignments must be used with caution in assigning nitrolic acid structures.

Aminolysis of Nitrolic Acids.—It has been found that primary and secondary amines react stereospecifically with benzonitrile oxides (generated from hydroximoyl chlorides) to give only the *Z*-amidoximes **21** in which the nucleophile and OH group are *cis*.[7] On reaction of acetohydroximoyl chloride **18** (0.40 mol



dm^{-3} in MeOH) with morpholine we obtained, on isolation, the corresponding *E*-amidoxime (**22**, R_2NH = morpholine). The formation of **22** follows a pathway involving rapid dehydrohalogenation of **18** to the nitrile oxide **19** which then undergoes stereospecific formation of **21**. However **21** is thermodynamically unstable relative to the *E*-isomer **22** (interconversion occurring on mild heating or on catalysis by acid (rapid even at pH 6) or on attempted separation of the isomers by chromatographic techniques).

We have also obtained the same product, **22**, on reaction of the acetonitrolic acid **20** or its *O*-acyl derivative **15** with morpholine under a variety of conditions. This is consistent with base-catalysed loss of NO_2^- from **20** to form the same intermediate (**19**) which undergoes trapping to **21** and isomerization to **22** as before. The *E* configuration for these amidoximes **22** is supported by the observed separation between the CH_2 signals for the morpholino group of *ca.* 0.8 ppm (typically *E*-amidoximes show a difference of *ca.* 0.73 whereas the *Z* isomers show only *ca.* 0.40 ppm).

Similar results were obtained on reaction of aryl nitrolic acids with amines. In the case of the *o*- and *m*-nitrophenyl derivatives

Table 3 Observed rate constants for the hydrolysis of the *E*-ester **15** in aqueous solution[a]

pH	$k_{obs}/10^{-4}$ s^{-1}
10.2	700
10.1	425
9.7	333
8.9	115
8.2	29
7.3	8.1
6.8	3.3

[a] Measured at 25 °C (μ = 1.0 KCl), zero buffer concentration.

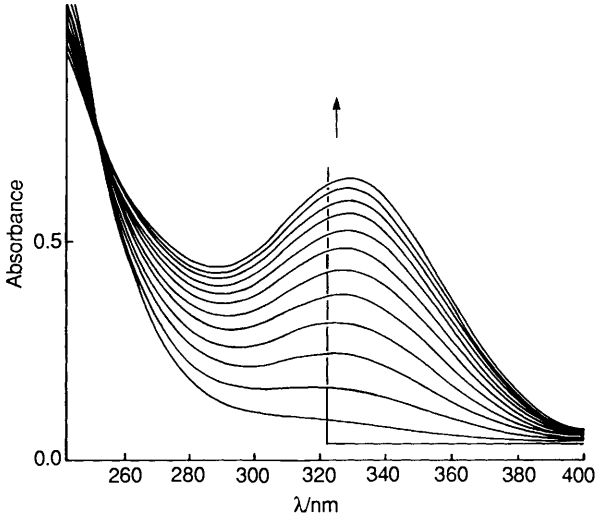
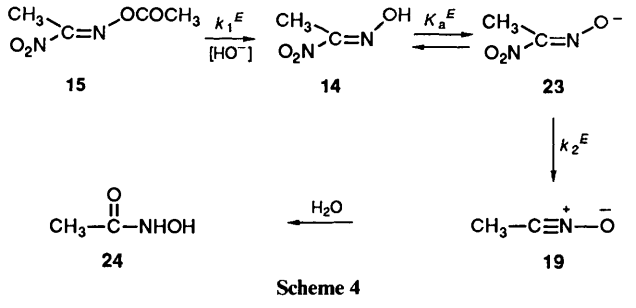


Fig. 3 Repetitive scans of the UV spectrum of the ester **15** as it is hydrolysed to the nitrolic acid anion **23** at pH 8.2 (μ = 1.0, KCl) at 25 °C. The scans were measured at 2 min intervals.

very mild reaction conditions (benzene at room temperature) yielded the intermediate *Z*-amidoximes (corresponding to **21**). Because of the known stereospecific reactions of nitrile oxides this adds support to the intermediacy of the corresponding arylnitrile oxides in these reactions.

Kinetic Results.—Aliphatic nitrolic acids and their esters. The rates of hydrolysis of the *E*- and *Z*-esters (**15** and **16** respectively) were followed spectrophotometrically in aqueous buffer solutions at 25 °C. For ester **15** repetitive scans in the λ = 400–250 nm region showed the appearance of a peak at 330 nm (Fig. 3). This reaction is base catalysed (see Table 3) but becomes pH independent at pH < 6. Buffer catalysis was also observed for this reaction and the observed rate constants quoted were obtained at zero buffer concentration.

This (first) reaction is hydroxide- and water-catalysed hydrolysis of the ester **15** to give (above pH 8) the nitrolic acid anion **23** or neutral species **14**. When the ester **15** was introduced into an aqueous buffer solution at pH > 10 and at 55 °C, initial ester hydrolysis was rapidly complete and a subsequent reaction (hydrolysis of the acetonitrolic acid **14**) was observed. The rates



Scheme 4

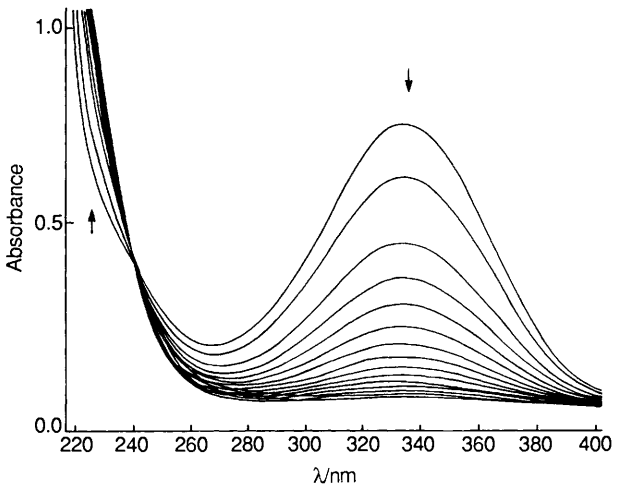


Fig. 4 Repetitive scans of the UV spectrum of the nitrolic acid anion **23** at pH 9.7 (carbonate buffer; μ = 1.0, KCl) at 55 °C. The product formed is acetohydroxamic acid. The scans were measured at 10 min intervals.

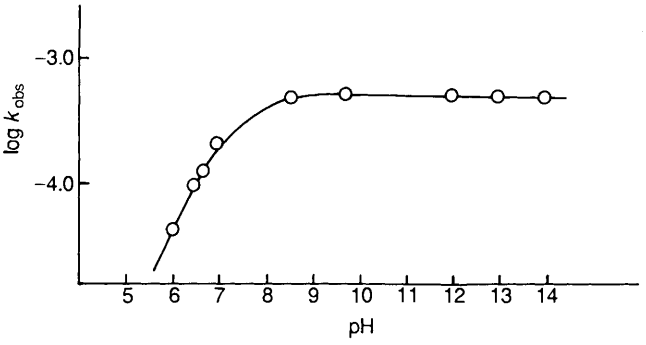


Fig. 5 Plot of log k_{obs} against pH for the hydrolysis of the nitrolic acid **14** [H_2O, μ = 1.0 (KCl)] at 55 °C

of this reaction are summarised in Fig. 5. That the species formed from **15** was the nitrolic acid **14** was confirmed by the direct measurement of the rates of reaction of **14** when introduced directly into aqueous solution; both sets of rate constants were identical when measured at various pH values. The rates of reaction of the nitrolic acid **14** were most conveniently followed by recording the disappearance of the characteristic absorption of the counter ion **23** (λ_{max} = 330 nm, see Fig. 4). The pH–rate profile observed for **14** is recorded in Fig. 5. This is consistent with unimolecular reaction of the mono-anion **23** at all pH values. The observed rate constants were correlated by eqn. (1) with k_2^E (the rate of NO_2^- loss from

$$k_{obs} = \frac{k_2^E \cdot K_a^E}{a_H + K_a^E} \quad (1)$$

the anion) = 4.6 × 10^{-4} s^{-1} and pK_a^E (the acidity of the nitrolic acid) = 7.25. It is seen from this that above pH *ca.* 7.5 the rate of loss of NO_2^- becomes pH independent, since under these conditions the anion **23** is the major species present.

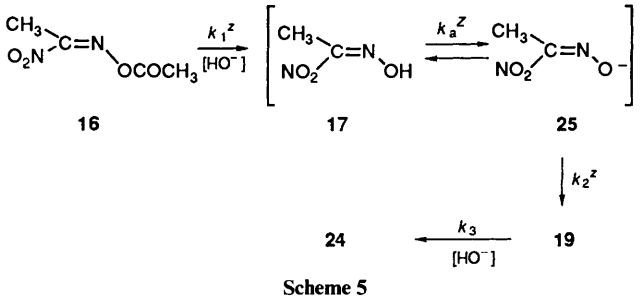
The product of hydrolysis of **14** is the corresponding hydroxamic acid **24** (the high dilution ensured that dimers were not formed). This was shown by spectral and chromatographic comparison at the end of reaction with an authentic sample. In theory the rates of reaction recorded in Fig. 5 could have been for subsequent reaction of the nitrile oxide **19** rather than NO_2^- loss from **23**. This possibility can however be ruled out since it has been previously shown that the rate of reaction of nitrile oxides such as **19** in aqueous solution is base catalysed at high pH. Moreover addition of morpholine (which at high concentration rapidly traps the nitrile oxide) did not affect the overall rate of reaction of **14** at high pH.

Table 4 Rate and equilibrium constants for arylnitrolic acids **26**

Nitrolic acid	k_2^E/s^{-1} [a]	pK_a^E [b]	$T/°C$
26a	4.5×10^{-4}	6.6	25
26b	4.0×10^{-4}	6.0	25
26c	5.7×10^{-4}	5.3	55

[a] Rate of formation of the 1,3-dipole from the anion. [b] Acidity constant (from kinetic data) for proton loss.

The results obtained for ester **16** were quite different. There was a fast initial reaction at 25 °C which could be measured at $\lambda = 265$ nm. However the absorbance change at all pH was very small indeed and there was no large absorption (corresponding to the anion **25**) at long wavelength. The observed rates of reaction were proportional to $[HO^-]$. We conclude that this represents rate determining ester hydrolysis; the rates of hydrolysis of the *E*- and *Z*-esters **15** and **16** were within a factor of two ($k_1^E = 4 \times 10^2$ dm^3 mol^{-1} s^{-1}; $k_1^Z = 3 \times 10^2$ dm^3 mol^{-1} s^{-1}).

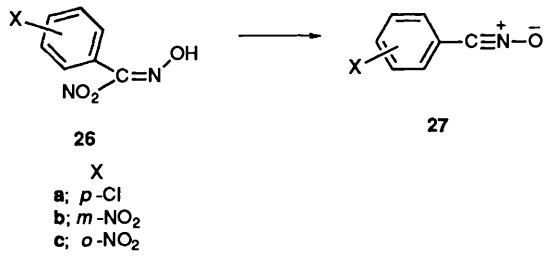


Scheme 5

In the pH region 10.5–13.0 a second subsequent reaction identified as hydrolysis of the nitrile oxide **19** to the acetohydroxamic acid **24** was observed; under these conditions initial deacylation of **16** was rapid. This reaction was followed at 235 nm and the observed rate of reaction ($k_3 = 6.2 \times 10^{-1}$ dm^3 mol^{-1} s^{-1} at 25 °C) obtained by extrapolation of a plot of k_{obs} *vs.* $[HO^-]$ to $[HO^-] = 1.0$ mol dm^{-3}; similar results (and spectral changes) were observed for the hydrolysis of the nitrile oxide, generated by rapid loss of HCl from the hydroximoyl chloride **18**. Again the addition of morpholine helped to clarify the kinetic behaviour of **16**. At pH 12.0, initial hydrolysis was accelerated to such an extent that the subsequent reaction of morpholine with the nitrile oxide **19** could be measured (the rate of which was proportional to morpholine free base concentration).

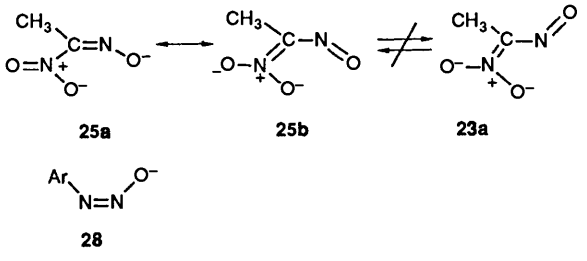
We therefore conclude that both esters **15** and **16** undergo ester hydrolysis at similar rates to give an observable nitrolic acid **14** only in the case of the *E*-ester **15**. The nitrolic acid **14** formed undergoes unimolecular loss of NO_2^- from the anion, presumably forming the nitrile oxide and ultimately aceto-hydroxamic acid. In the case of **16**, the nitrile oxide could not be observed as an intermediate so that, even at high pH where the ester hydrolysis is fast, breakdown of the anion **25** to **19** was too fast to measure. However in this case we were able to confirm the intermediacy of the nitrile oxide by directly measuring its reactions with HO^- and with morpholine.

Arylnitrolic acids. *m*-Nitro-, *o*-nitro- and *p*-chloro-benzo-nitrolic acids were isolated as single isomers [by dissolution in base and rapid reprecipitation with acid or directly on the reaction with nitrogen dioxide (for **26c**)]. pH–log rate profiles were constructed for the reactions of each in the pH region 5.0–14.0. A single reaction was observed in each case and the behaviour observed at 25 °C was broadly similar to that for the *E*-isomer **14** of acetonitrolic acid. The derived acidity and rate constants for these nitrolic acids is summarised in Table 4. The *o*-nitroisomer reacts more slowly (Table 4); note that these data were measured at 55 °C. We conclude that these therefore have the *E* (*i.e.* slowly reacting) configuration.



Scheme 6

In conclusion, deprotection of (*E*)- and (*Z*)-O-acetylnitrolic acids, **15** and **16** in basic solution leads to the corresponding nitrolic acid **14** and **17** respectively. The *E*-nitrolic acid **14** (in which the lone pair is synperiplanar to the leaving group) undergoes NO_2^- loss at a measurable rate from the corresponding anion (formed at pH > 7). The *Z*-nitrolic acid undergoes NO_2^- loss more rapidly so that the only reaction followed on deprotection of **16** is reaction of HO^- with the acetonitrile oxide **19** formed. Photoisomerisation of protected nitrolic acids therefore constitutes a good route to these 1,3-dipoles. Since the *E* and *Z* anions **23** and **25** react at markedly different rates they do not rapidly interconvert. This may appear surprising since **25b** should be a major contributor and



28

isomerization to **23a** involves C–N bond rotation; however the related diazotates **28** show similar configurational stability.

Most synthetic procedures lead to mixtures of *E*- and *Z*-isomers of nitrolic acids. The (less reactive) *E*-isomer can be separated by dissolution of the mixture in basic solution (when the *Z*-isomer undergoes rapid elimination and subsequent dimerization) followed by reprecipitation in acid. The measured rates of reaction for the *E*-isomer reported here allows the calculation of the optimum residence time in basic solution. Moreover this report also draws attention to the marked dependence of nitrolic acid reactivity on configuration which may be critical when these are involved as intermediates in nitric acid oxidation of alkanes.

Experimental

General.—M.p.s were determined in a Kofler hot-stage apparatus and are uncorrected. UV spectra for product analysis were run on a Cary Model 210 spectrophotometer. A Perkin-Elmer R12 NMR spectrometer or JEOL GX 270 NMR spectrometer was used with $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Combustion analyses were carried out at the Microanalytical Laboratory, UCD. Water was doubly distilled from an all-glass apparatus before use and dioxane was Merck pure grade, distilled from calcium hydride and stored over sodium wire. Dinitrogen tetraoxide was supplied by BDH. All *J* values are given in Hz.

Substrates.—The oximes used [including (*E*)- and (*Z*)-

Table 5 Physical and analytical data for nitrolic acids. $RC(NO_2)=NOH$

R	M.p./°C	δ	Microanalysis Found (%) C	H	N	Cl	Formula	Requires (%) C	H	N	Cl
C_6H_5	56–58	74.45–7.65 (5 H, m)	50.13	3.84	16.31	—	$C_7H_6N_2O_3$	50.60	3.6	16.86	—
p-$NO_2C_6H_4$	55	7.85–8.8 (4 H, m) 13.5 (1 H, s); 8.32 (2 H, HBB′); 7.79 (2 H, HAA′)	40.94	2.65	18.29	—	$C_7H_5N_3O_5$	39.80	2.36	19.9	—
m-$NO_2C_6H_4$[a]	68–70	7.13–8.06 (4 H, m) 13.29 (1 H, s)	36.81	2.67	18.18	—	$C_7H_5N_3O_5$	39.80	2.36	19.9	—
o-$NO_2C_6H_4$	79–81	7.0–7.7 (4 H, m)	39.00	2.35	19.2	—	$C_7H_5N_3O_5$	39.80	2.36	19.9	—
p-ClC_6H_4	—	6.9–7.5 (m); 7.2 (s); 9.45 (s)	41.96	2.18	13.50	17.65	$C_7H_5ClN_2O_3$	41.90	2.51	13.97	17.68
CH_3	84–85	2.53 (3 H, s)	22.96	4.3	26.55	—	$C_2H_4N_2O_3$	23.00	3.84	26.9	—

[a] Analysis indicated water of crystallization present.

benzaldehyde oxime] were prepared by a literature procedure and had the expected physical data.

p-*Nitrobenzonitrolic acid.* A solution of *p*-nitrobenzaldehyde oxime (5.0 g) in dry ether (50 cm^3) was cooled to 0 °C and dinitrogen tetraoxide (1.37 g) was added. The reaction mixture became green in colour and a precipitate appeared. After 1 h at 20 °C the precipitate was removed by filtration. The filtrate was diluted with hexane (75 cm^3) washed with water and filtered again. The filtrate was evaporated at 0 °C to give the nitrolic acid as yellow crystals, (see Table 6) residual water being removed *in vacuo* without heating. Attempts to remove water using $MgSO_4$ as a drying agent led to decomposition. The *p*-chloro, *o*-nitro and *m*-nitro analogues were similarly prepared (see Table 5).

Benzonitrolic acid. To a solution of (*E*)-benzaldehyde oxime (5 g, 0.02 mol) dissolved in ether (200 cm^3) at reflux was added a solution of dinitrogen tetraoxide (2.1 g, 0.022 mol) in ether (10 cm^3) at a rate such that a gentle reflux was maintained (over about 3 min). The solution was refluxed for 3 min and then ice (50 g) was added. The ethereal layer was separated and washed once with water and then extracted with cold 4% aqueous ammonium hydroxide. The red alkaline solution obtained (100 cm^3) was washed with ether (100 cm^3) and then covered with ether while being neutralized with oxalic acid at 0 °C. The solution is self-indicating, the colour disappearing on neutralization. The aqueous solution was then extracted with ether (50 cm^3) and the extract after washing with ice-cold water and drying ($MgSO_4$) was evaporated to give benzonitrolic acid as pale yellow needles (Table 5). The arylnitrolic acids were not stable at room temperature and were stored at −15 °C.

Acetonitrolic acid. Sodium nitrite (1.0 g) was added to nitroethane (1.0 g) in 20% aqueous sodium hydroxide (10 cm^3) at 0 °C. An ice-cold solution of sulphuric acid (3 mol dm^{-3}) was added slowly. The mixture was then made alkaline with 4% aqueous ammonium hydroxide. The solution, which was then an intense red colour, was covered with ether and brought at 0 °C to pH 6 using oxalic acid. The aqueous solution was extracted with ether (50 cm^3) and the combined ether extracts were washed with ice-cold water and dried (10 min) over magnesium sulphate. Acetonitrolic acid was isolated on evaporation of the ether as a pale yellow solid (see Table 5); it showed better thermal stability than the aromatic analogues.

Separation of E/Z *Isomers of the Arylnitrolic Acids.*—While *o*-nitrobenzonitrolic acid was obtained in a single isomeric form, the other arylnitrolic acids were isolated as an isomeric mixture. In the case of *p*-chloro- and *m*-nitro-benzonitrolic acid, a mixture of the two forms was introduced in 10% aqueous potassium hydroxide, cooled to 0 °C. The red-orange solution thus obtained was filtered from the precipitated decomposition products of the *Z*-form of the nitrolic acid. The filtrate was acidified carefully with 5% aqueous hydrochloric acid at 0 °C. The resulting pH of the solution was six. The precipitate formed was isolated by filtration, washed with water and dried under high vacuum (0.1 mmHg). This gave a single isomeric form of *p*-chloro- and *m*-nitro-benzonitrolic acid in a yield of 40%. The products were not stable at room temperature, as a result they were stored below 0 °C at all times.

Similar treatment of the two forms of *p*-nitrobenzonitrolic acid resulted in a mixture, but on storage at −15 °C for several weeks the NMR spectrum indicated that the acid was present in a single isomeric form.

Ester Derivates of E-*Acetonitrolic Acid.*—Distilled acetyl chloride (0.02 mol) was dissolved in dry benzene (20 cm^3), the solution was cooled on an ice bath. (*E*)-Acetonitrolic acid (0.01 mol) was added. This was followed by dropwise addition of triethylamine (0.02 mol). The reaction mixture was stirred at room temperature for 1 h and then poured into ice. The organic portion was extracted into ether, separated, and dried ($MgSO_4$). After filtration the solvent was removed *in vacuo* leaving a liquid residue. The desired *product* was obtained pure by preparative TLC on silica gel; eluent 1:1 ether:light petroleum (40–60 °C). (Found: C, 32.5; H, 3.8; N, 18.9. $C_4H_6N_2O_4$ requires C, 32.8; H, 4.1; N, 19.2%); δ_H 2.71 (3 H, s) and 2.45 (3 H, s); ν_{max}/cm^{-1} 1810.

O-*Acetylphenylnitrolic acid* was prepared similarly: (Found: C, 52.2; H, 4.3; N, 13.1. $C_9H_8N_2O_4$ requires C, 51.9; H, 3.85; N, 13.5%); δ_H 7.2–7.6 (5 H, m) and 2.0 (3 H, s); ν_{max}/cm^{-1} 1770.

Isomerization of O-*Acetyl-acetonitrolic Acid.*—The *O*-acetyl derivative was dissolved in dry benzene (10 cm^3). This solution was irradiated in a water-cooled quartz reaction vessel with a 450 W UV lamp. Irradiation for 24 h gave 100% conversion into the *Z*-isomer. The benzene was then removed *in vacuo*, leaving a residual oil. The desired *product* was separated from a coloured impurity by preparative TLC on silica gel; eluent: 1:1 ether:light petroleum (Found: C, 33.0; H, 3.8; N, 19.2. $C_4H_6N_2O_4$ requires C, 32.8; H, 4.1; N, 19.2%); δ_H 2.63 (3 H, s) and 2.30 (3 H, s); ν_{max}/cm^{-1} 1800.

Acetohydroximoyl Chloride.—Acetaldehyde oxime (10 g) was dissolved in dry ether (150 cm^3); the solution was cooled to −60 °C, using a chloroform–liquid nitrogen slurry. The acetaldehyde oxime had been twice distilled prior to use. A steady stream of chlorine gas was passed through the cooled solution. The solution turned a deep green-blue colour, and a

Table 6 Final atomic co-ordinates in (*E*)-acetonitrilic acid **14**

	x	*y*	*z*
O(1)	−0.197 5(5)	−0.024 1(3)	−0.442 83(21)
N(1)	−0.141 4(5)	−0.082 9(3)	−0.540 53(24)
O(2)	−0.264 9(5)	−0.198 9(3)	−0.586 35(23)
C(1)	0.093 8(7)	−0.010 7(4)	−0.609 2(3)
N(2)	0.203 6(6)	0.112 4(3)	−0.556 63(23)
C(2)	0.161 1(8)	−0.090 4(4)	−0.724 5(3)
O(3)	0.426 2(5)	0.177 2(3)	−0.619 97(21)

white precipitate also formed. After 30 min the flow of chlorine gas was stopped, and the blue ether solution was separated from the precipitate by filtration. The ether solvent was removed on a rotatory evaporator at 0 °C, leaving a white solid (the chloro–nitroso dimer). The dimer (0.2 mol dm^{-3}) was dissolved in dry methanol at 0 °C; this yielded a blue solution which, after being left at 0 °C for several hours, became colourless. This is indicative of the isomerization to the desired acetohydroximoyl chloride. NMR spectra in methanol indicated the presence of 1-chloro-1-nitrosoethane which is in equilibrium with its dimer. This gave a blue solution in deuteriochloroform which, after it had been left at 0 °C, became colourless. The NMR spectrum then showed an additional peak attributable to the desired hydroximoyl chloride; dimethyl furoxan was formed from this ultimately; δ_H 6.80, 6.66 (1 H, two q, J = 6.8), 1.96 (1 H, d, J = 6.5, 1-chloro-1-nitrosoethane and its dimer), 2.40 (3 H, s, acetohydroximoyl chloride), 2.80 (3 H, s) and 2.60 (3 H, s, dimethylfuroxan).

Amidoximes.—Reaction of morpholine with acetohydroximoyl chloride. Morpholine (7 g) was dissolved in dry benzene (15 cm^3) and the solution cooled to −5 °C; a methanol solution of acetohydroximoyl chloride was added dropwise. On stirring at room temperature for 2 h, the morpholine hydrochloride precipitated from solution. The reaction mixture was poured into ether–water mixture, the ether layer was separated and dried ($MgSO_4$). After filtration the ether was removed on a rotatory evaporator, excess morpholine was removed under high vacuum (0.1 mmHg) at 25 °C to yield the *amidoxime* as a white solid m.p. 70–72 °C (from hexane:chloroform) (Found: C, 49.5; H, 8.2; N, 18.8. $C_6H_{12}N_2O_2$ requires C, 50.00; H, 8.33; N, 19.4%); δ_H 3.98 (4 H, m), 3.18 (4 H, m) and 2.24 (3 H, s); ν_{max}/cm^{-1} 3250 and 1630. The (*Z*)-*O*-acetylacetonitrolic acid was reacted under the same conditions to give the same product. (*E*)-Acetonitrolic acid gave the same product except that the benzene solution had to be refluxed overnight to complete the reaction.

Morpholino-o-nitrobenzamidoxime. *o*-Nitrobenzonitrolic acid (0.5 g) in dry benzene was added to a benzene solution of dry morpholine (5 g). The reaction mixture was refluxed overnight. The crude product was isolated as outlined previously and purified by preparative TLC on silica gel, (eluent 1:1 petroleum spirit:ether). Recrystallization from a hexane–chloroform mixture gave pure *amidoxime* product m.p. 190–192 °C; (Found: C, 52.2; H, 5.4; N, 16.3. $C_{11}H_{13}N_3O_4$ requires C, 52.5; H, 5.3; N, 16.7%); δ_H 7.0–7.7 (4 H, m), 3.18 (4 H, m) and 2.5 (4 H, m).

(*Z*)-*Morpholino*-p-*nitrobenzamidoxime.* This was prepared similarly (but the reaction mixture was stirred at room temperature for 2 h) and had m.p. 170–172 °C (Found: C, 52.1; H, 5.1; N, 16.35. $C_{11}H_{13}N_3O_4$ requires C, 52.6; H, 5.2; N, 16.7%); δ_H 8.35 (2 H, BB1), 7.8 (2 H, AA1), 3.82 (4 H, m) and 3.46 (4 H, m).

(*Z*)-*Morpholino*-m-*nitrobenzamidoxime* similarly prepared had m.p. 125–127 °C (Found: C, 52.0; H, 5.2; N, 16.1); δ_H 7.43–8.63 (5 H, m), 3.80 (4 H, m) and 3.43 (4 H, m).

Kinetic Method.—The course of the reactions was followed on a Cary Model 210 spectrophotometer. Repetitive scans of the UV-VIS region (λ/nm 400–200) established suitable wavelengths at which the reaction rates could be measured. In the case of the nitrolic acids, reactions were initiated by injecting 20 mm^3 of a 1 × 10^{-2} mol dm^{-3} solution of substrate in dried dioxane into a cell containing an aqueous solution (2 cm^3) buffered at the appropriate pH. The stock solution, (1 × 10^2 mol dm^{-3}) of the acetohydroximoyl chloride was made up in dried methanol. Initial experiments established that the reactions were not buffer catalysed. The morpholine water mixtures were prepared by mixing appropriate volumes of the component solvents at room temperature. The morpholine had been purified by distillation. The temperature was maintained at 25 °C for most reactions; 40–55 °C was used for some slower reactions. Good first order rate constants (±3% on repeat runs) were obtained using experimental infinity values. Potassium chloride or sodium perchlorate were used to maintain the ionic strength at unity.

Crystallographic Study.—A single crystal of essentially colourless acetonitrolic acid **14** was removed from cold storage, rapidly mounted in a Lindemann capillary, and introduced into the cold stream (N_2 gas) of an Enraf-Nonius CAD4 diffractometer fitted with a ULT-2 low temperature device.

Crystal data. $C_2H_4N_2O_3$, M = 104.05, orthorhombic, space group $P2_12_12_1$, a = 4.7847(24), b = 7.997(4), c = 11.240(3) Å, U = 430.1 $Å^3$ at 185 ± 1 K, from the centring of 25 strong reflections, 13° < θ < 15°, Z = 4, D_c = 1.607 g cm^{-3}, graphite-monochromated Mo-Kα X-radiation, λ_{av} = 0.710 69 Å, ν(Mo-Kα) = 1.41 cm^{-1}; $F(000)$ = 216.

Data collection and reduction. ω–2θ scans in 96 steps, ω scan width 0.8 + 0.35 tanθ, 1 ≤ θ ≤ 25°, *h*0–5, *k*0–9, *l* − 13–13, scan speeds 1.27–5.49° min^{-1}. 927 data measured over *ca.* 16 X-ray h, no detectable decay or movement. 668 reflections retained with $F \geq 2.0\sigma(F)$.

Solution and refinement. Structure solved by automatic direct methods using SHELX84,[24] affording all non-H atom positions. H atoms located from subsequent ΔF synthesis following full-matrix least-squares refinement. In the final stages all non-H atoms refined with anisotropic thermal parameters. H atoms given a fixed isotropic thermal parameter of 0.04 $Å^2$. Weighting scheme $w^{-1} = \sigma^2(F) = 0.0089\,F^2$. R = 0.0537, R_w = 0.0708, S = 0.709. Max. and min. residues in final ΔF map 0.26 and −0.32 e $^{-3}$. Non-hydrogen atomic co-ordinates are given in Table 6. Anisotropic thermal parameters and hydrogen atomic co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.* Computer programs used in addition to that referenced above: CADABS,[25] SHELX76,[26] CALC[27] and EASYORTEP.[28] Atomic scattering factors were those inlaid in SHELX.

* For details of the CCDC deposition scheme see 'Instructions for Authors (1991),' *J. Chem. Soc., Perkin Trans. 2*, Issue 1.

References

1 M. Yotsumiya and R. Harada, Jap. P33725 1973 (*Chem. Abstr.*, 1974, **80**, 12091).

2 (*a*) V. I. Trubnikova, V. A. Preobrazhenskii, A. M. Goldman, M. S. Furman and V. N. Kostina, *Khim. Promst. (Moscow)*, 1970, **46**, 12 (*Chem. Abstr.*, **72**, 120809); (*b*) *Zh. Prikl. Khim. (Leningrad)*, 1974, **47**, 2272 (*Chem. Abstr.*, **82**, 30708).

3 T. Osawa, H. Ishibashi, M. Namiki, T. Kada and K. Tsuji, *Agric. Biol. Chem.*, 1986, **50**, 1971; P. E. Hartman, *Environ. Mutagens., Proc. Ann. Meet. Eur. Environ. Mutagens. Soc. 6th*, 1983, **5**, 217; A. Mirna. *Arch. Lebensmittelhyg.*, 1982, **33**, 95; M. C. Robach, V. G. DiFate, K. Adam and L. K. Kier, *Food Cosmet. Toxicol.*, 1980, **18**, 237.

4 K. N. Korotaevskii, E. N. Zil'berman, N. K. Petrova, I. Y.

Lubyanitskii, V. K. Fukin and G. N. Matvbeeva, *Zh. Org. Khim.*, 1977, **13**, 1814.
5 K. N. Korotaevskii, E. N. Zil'berman and I. Y. Lubyanitskii, *Zh. Fiz. Khim.*, 1977, **51**, 2958.
6 A. F. Hegarty and M. Mullane, *J. Chem. Soc., Chem. Commun.*, 1984, 229.
7 A. F. Hegarty and M. Mullane, *J. Chem. Soc., Perkin Trans. 2*, 1986, 995.
8 E. Bamberger and R. Seligman, *Ber. Dtsch. Chem. Ges.*, 1902, **35**, 3884.
9 (*a*) L. I. Khmelnitskiik, S. S. Novikov and O. V. Lebedev, *Izv. Akad. Nauk., SSSR, Ser. Khim.*, 1961, 477 (*Chem. Abstr.*, 1961, **55**, 23389); (*b*) L. I. Khmelnitskiik, S. S. Novikov and O. V. Lebedev, *Zh. Obshch. Khim.*, 1958, **28**, 2303 (*Chem. Abstr.*, 1959, **53**, 3111).
10 L. I. Khmelnitskiik, S. S. Novikov and O. V. Lebedev, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1960, 1783 (*Chem. Abstr.*, 1961, **55**, 1983).
11 A. I. Titov and V. V. Siminov, *Dokl. Akad. Nauk. SSSR*, 1952, **83**, 243 (*Chem. Abstr.*, 1953, **47**, 4298).
12 S. S. Novikov, O. V. Kebedev, L. I. Khmelnitskii and Yu. P. Egorov, *Zh. Obshch. Khim.*, 1958, **28**, 2305 (*Chem. Abstr.*, 1959, **53**, 4112).
13 R. Scholl, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 3496.
14 J. H. Boyer and H. Alul, *J. Am. Chem. Soc.*, 1959, **81**, 4237.
15 A. Hantzsch and H. Kissel, *Ber. Dtsch. Chem. Ges.*, 1899, **32**, 3137.
16 L. Zublin, *Ber. Dtsch. Chem. Ges.*, 1877, **10**, 2083.
17 V. Meyer, *Ber. Dtsch. Chem. Ges.*, 1873, **6**, 1492.
18 V. Meyer, *Ann. Chem.*, 1875, **175**, 88.
19 L. I. Khmelnitskii, O. V. Lebedev, V. I. Slovetskii and S. S. Novikov, *Izv. Akad. Nauk. SSSR*, 1961, **4**, 678.
20 J. E. Johnson, E. A. Nalley, Y. K. Kunz and J. R. Springfield, *J. Org. Chem.*, 1976, **41**, 252.
21 S. Shiotani, H. Morita, M. Inoue, T. Ishida, Y. Iitaka and A. Itai, *J. Heterocycl. Chem.*, 1984, **21**, 725.
22 T. J. Cholerton, J. Clitherown, J. H. Hunt, J. W. M. Mackinnon, M. Martin-Smith, B. J. Price, J. Murray-Rust and P. Murray-Rust, *J. Chem. Res. (M)*, 1985, 2818.
23 D. I. Morgan, *J. Appl. Chem.*, 1959, **9**, 201.
24 G. M. Sheldrick, University of Gottingen, 1986.
25 R. O. Gould and D. E. Smith, University of Edinburgh, 1986.
26 G. M. Sheldrick, University of Cambridge, 1976.
27 R. O. Gould and P. Taylor, University of Edinburgh, 1986.
28 P. D. Mallinson and K. W. Muir, *J. Appl. Crystallogr.*, 1985, **18**, 51.

Paper 0/03004J
Received 4*th July* 1990
Accepted 31*st August* 1990