Antiparasitic Nitroimidazoles. Part II.[1] The Decomposition of 5-Nitro-2-(4-*trans*-styryl)-1-vinylimidazoles by Sodium Hydroxide

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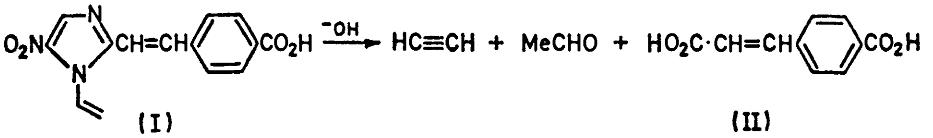
trans-4-[2-(5-Nitro-1-vinylimidazol-2-yl)vinyl]benzoic acid (I) decomposes in alkaline solution to 4-carboxycinnamic acid, acetaldehyde, and acetylene. The rate of the reaction is of the first order in both the imidazole and the hydroxide ion concentration. In 50% aqueous dimethyl sulphoxide containing tetramethylammonium hydroxide, changes of the substituent in the styryl group exert little variation on the rate coefficient for decomposition, whilst changes in the 1-substituent induce significant reactivity variations. These results are interpreted as indicative of initial hydroxide attack at the 4-position, followed by rate-determining opening of the imidazole ring.

In Part I[1] the synthesis and antiparasitic activity of a series of substituted nitroimidazoles was discussed. This paper is concerned with the alkaline instability of a number of these compounds.

The reactions of aromatic nitro-compounds with basic reagents have attracted considerable interest.[2] Studies with heteroaromatic compounds have been mainly confined to pyridine and triazine derivatives,[3] and by comparison five-membered heterocycles containing nitro-groups have received little attention. Sunjić and his co-workers have reported the reaction of 1,2-dimethyl-5-nitroimidazole with 5% sodium hydroxide in ethanol.[4] An intensely red solution, attributed to Meisenheimer-complex formation, developed on heating the reactants. As the colour faded, ammonia was evolved but no other product was identified. We have found that the acid (I) is decomposed by sodium hydroxide in aqueous solution.



(I) (II)

Under preparative conditions, aqueous solutions of compound (I) (pH 8—9) darken rapidly and gases are evolved on addition of sodium hydroxide (pH 11—14). Spectral analysis of the residue, obtained from the chloroform extracts of the acidified reaction solution, enables 4-carboxy-*trans*-cinnamic acid to be identified as the sole solid product. Estimation of the acid as its dimethyl ester by g.l.c. shows it to be formed in yields of 80—90%. The gaseous components were isolated by running the alkaline decomposition under reduced pressure, when the reaction solution develops much less colour than at atmospheric pressure. The gases were collected in a large flask, which was sealed, and the components were analysed by g.l.c. and mass spectrometry. The g.l.c. retention times were identical to those of acetylene and acetaldehyde and identification of these products was confirmed by accurate mass measurements. Removal of acetaldehyde from the alkaline solution accounts for the reduction in the dark colour when the reaction is carried out under reduced pressure. The ratio of acetaldehyde to acetylene cannot be assessed with certainty under the experimental conditions, but the former seems to predominate.

The rate of decomposition of (I) can be monitored conveniently by visible spectroscopy at its wavelength of maximum absorption (370 nm). In this region the carboxycinnamic acid (II) does not absorb and, in the dilute solutions used for spectroscopic studies, acetaldehyde polymerisation does not complicate the measurements.

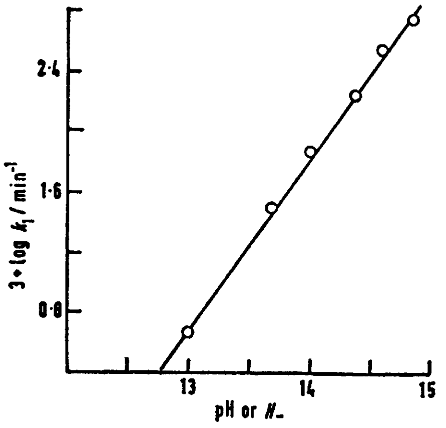


FIGURE 1 Variation in the rate of hydrolysis of compound (I) with the basicity of the reaction medium as measured by pH or H_-. k_1 is the pseudo-first-order rate coefficient for hydrolysis in aqueous solution at 30 °C; H_- (ref. 5) is used for pH greater than 14; slope = 1·127 ± 0·022, correlation coefficient = 0·9993, F-ratio = 2531

The rate of decomposition is of the first order in both the concentration of (I) and hydroxide ion (estimated by pH or H_-[5] as appropriate) for the pH region 11—15 (see Figure 1 and Table 1). This observation is consistent with a rate-determining hydroxide attack on the imid-

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[1] Part I, W. J. Ross and W. B. Jamieson, *J. Medicin. Chem.*, in the press.

[2] M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211.

[3] G. Illuminati, *Adv. Heterocyclic Chem.*, 1964, **3**, 285.

[4] V. Sunkić, R. Fajdiga, M. Japelj, and P. Rems, *J. Heterocyclic Chem.*, 1969, **6**, 53.

azole or a rapid equilibrium involving hydroxide addition, followed by a unimolecular decomposition of the addition product.

The product analysis and the kinetic order for the alkaline decomposition of compound (I) can be explained by initial hydroxide attack at the 2- or the 4-position of the imidazole ring or the *N*-vinyl group. Of these, attack on the *N*-vinyl group, resulting in acetylene elimination, seems least probable, as this would lead to formation of the sodium salt of the imidazole, of which a number of analogues are known to be stable.[6] To distinguish between the other possibilities, the rate coefficients for hydrolysis of a series of substituted 5-nitro-2-styryl-*N*-vinylimidazoles were determined. Because of insolubility in aqueous solution, 50% aqueous dimethyl sulphoxide was used and the results in Table 2 clearly demonstrate the absence of a significant substituent effect. Both electron-withdrawing and electron-releasing substituents increase the reaction rate relative to the unsubstituted styryl compound, but only to a very limited extent. If hydroxide attack occurred at the 2-position a much larger substituent effect would be expected. For example, a reaction constant of 0·418 is observed in the ionisation of substituted *trans*-cinnamic acids.[7]

TABLE 1

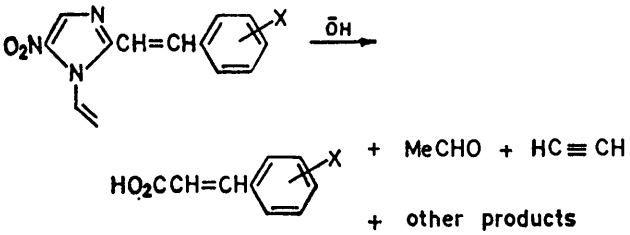
Rate coefficients for hydrolysis of the acid (I) in aqueous solutions of sodium hydroxide at 30 °C

pH ‡	10^3k_1/min^{-1}	pH ‡	10^3k_1/min^{-1}
14·83	554	13·99	74·6
14·62	348	13·69	31·6
14·37	175	12·98	4·57

‡ pH calculated from the molarity of sodium hydroxide. Values greater than pH = 14·00, are H_- values obtained from ref. 5. Rate coefficients are accurate to ±2%.

TABLE 2

Rate coefficients for the decomposition of substituted 5-nitro-2-styryl-*N*-vinylimidazoles with $^+NMe_4OH^-$ in 50 mol % dimethyl sulphoxide–water at 30 ± 0·1 °C; $[NMe_4OH] = 1·18 \times 10^{-1}$M



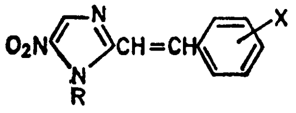
X	$10k_1$/min^{-1}	X	$10k_1$/min^{-1}
4-CO_2^-	1·45	4-Cl	1·72 ± 0·02
H	1·50 ± 0·02 ‡	4-OMe	2·27 ± 0·02
3-CF_3	1·80	4-Me	1·69 ± 0·02
3,4-Cl_2	1·97 ± 0·04	4-CN	1·97 ± 0·02

‡ Mean of two runs with average deviation.

Changes in the *N*-substituent cause significant variations in the rate of decomposition of the styrylimidazoles by hydroxide ion (see Table 3). However, the two-fold difference in hydrolysis rate between the *N*-vinyl and *N*-*trans*-prop-2-enyl compounds is too small for attack in the rate-determining step to occur at the *N*-substituent. For the *N*-vinyl compound, acetylene formation can occur by an *anti*-elimination, but methylacetylene formation from the propenyl compound is confined to a *syn*-elimination pathway. The $k_{anti}:k_{syn}$ ratios for alkyne formation in protic solvents are generally much greater[8] than a factor of *ca.* 2.

TABLE 3

Rate coefficients for hydrolysis of *N*-substituted 5-nitro-2-styrylimidazoles with $^+NMe_4OH^-$ in 50 mol % dimethyl sulphoxide–water at 30 ± 0·1 °C; $[NMe_4OH] = 1·18 \times 10^{-1}$M



R	X	10^3k_1/min^{-1}
CH=CH_2	H	150 ± 2
trans-CH=CHMe	H	67·5 ± 0·4
Me	H	5·30 ± 0·12
Et	H	2·53 ± 0·08
CH_2·CH_2OH	H	6·42 ± 0·12
CH_2·CH_2OH	4-Cl	7·32 ± 0·10
CH_2·CH_2OH	4-OMe	5·39 ± 0·10

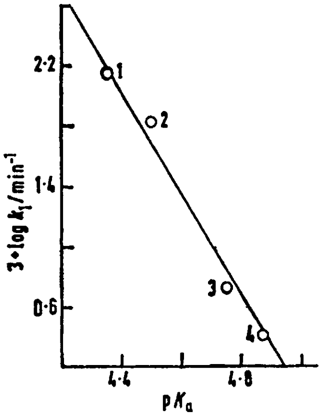


FIGURE 2 Correlation of rates of hydrolysis of *N*-substituted 5-nitro-2-styryl imidazoles by hydroxide ion in 50 mol % dimethyl sulphoxide–water at 30 °C with pK_a values of the corresponding carboxylic acids. pK_a values of the carboxylic acids in water at 25 °C are as follows: AcOH, 4·75; $EtCO_2H$, 4·87 (G. Kortum, W. Vogel. and K. Andrussow, 'Dissociation Constants of Organic Acids in Solution,' Butterworths, London, 1961); $H_2C{=}CH{\cdot}CO_2H$, 4·35; *trans*-MeCH=CH·CO_2H, 4·51 (M. Charton, *J. Org. Chem.*, 1964, **29**, 1222; the *N*-substituents are as follows: 1, CH_2=CH; 2, *trans*-MeCH=CH; 3, Et; 4, Me; Slope = −3·61 ± 0·33, correlation coefficient = 0·9913, *F*-ratio = 114·7

The enhanced reactivity of the *N*-vinyl compounds relative to the *N*-alkyl derivatives can be ascribed to

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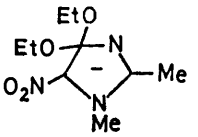
[5] K. Bowden, *Chem. Rev.*, 1966, **66**, 119.

[6] L. V. Epishina, V. I. Slovetskii, V. G. Osipov, O. V. Lebedev, L. I. Khmel'nitskii, V. V. Sevost'yanova, and T. S. Novikova, *Khim. Geterotsikl. Soedin.*, 1967, **4**, 716 (*Chem. Abs.*, 1968, **68**, 68,249*x*).

[7] K. Bowden, *Canad. J. Chem.*, 1963, **41**, 2781.

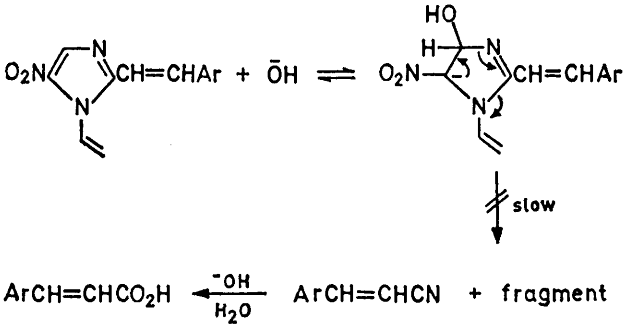
[8] S. J. Cristol and W. P. Norris, *J. Amer. Chem. Soc.*, 1954, **76**, 3005.

the greater electron-withdrawing power of the unsaturated substituents. Electron withdrawal by reducing



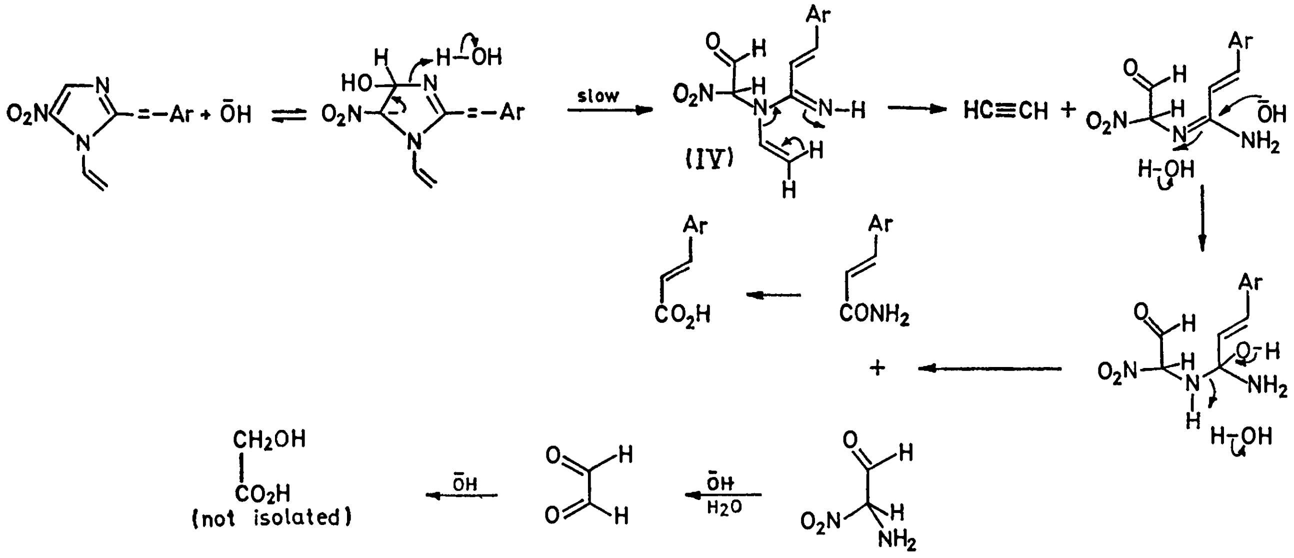
(III)

the electron density in the imidazole ring system increases its activity towards nucleophilic reagents.



SCHEME 1

In fact, the rates of hydrolysis of the various N-substituted imidazoles correlate quite well with the pK_a values of the corresponding substituted carboxylic acids (see Figure 2).



SCHEME 2

The above kinetic results suggest that initial hydroxide attack occurs at the 4-position of the 5-nitro-2-styryl-N-substituted imidazoles. It seems reasonable to predict that only a low concentration of hydroxide addition intermediate is formed under our reaction conditions.* Subsequent ring opening then occurs in the rate-determining step. The carboxycinnamic acid product does not arise *via* the corresponding cinnamyl cyanide, as the latter hydrolyses much more slowly than any of the nitroimidazole compounds under identical conditions of medium basicity (Scheme 1). Ring opening most probably results in the formation of amidine (IV), which should hydrolyse rapidly in the presence of hydroxide,[9] fragmenting to acetylene (Scheme 2) and acetaldehyde (Scheme 3) and the cinnamide. The hydrolysis of the last compound was too rapid to follow under the reaction conditions used to hydrolyse the imidazoles.

Our suggested mechanism requires branching of pathways at the amidine (IV). Both acetylene (Scheme 2) and acetaldehyde (Scheme 3) originate from the N-vinyl substituent, and neither evolves from the imidazole ring carbons. Studies on the N-ethyl compound support this prediction. Neither acetaldehyde nor acetylene were found in the decomposition of this substrate and the basic gas detected by a moist pH paper, but not actually isolated, is probably ethylamine.

EXPERIMENTAL

Preparation of Reagents.—*Styrylimidazoles*. All the styrylimidazoles were kindly supplied by Dr W. J. Ross and Mr W. B. Jamieson. They were prepared by condensation of the corresponding aldehyde and 2-methyl-5-nitro-N-substituted imidazole by methods described previously.[1,10] All samples had satisfactory microanalyses and spectra. The imidazole and aryl groups were *trans*-related across the styryl double bond as shown by the

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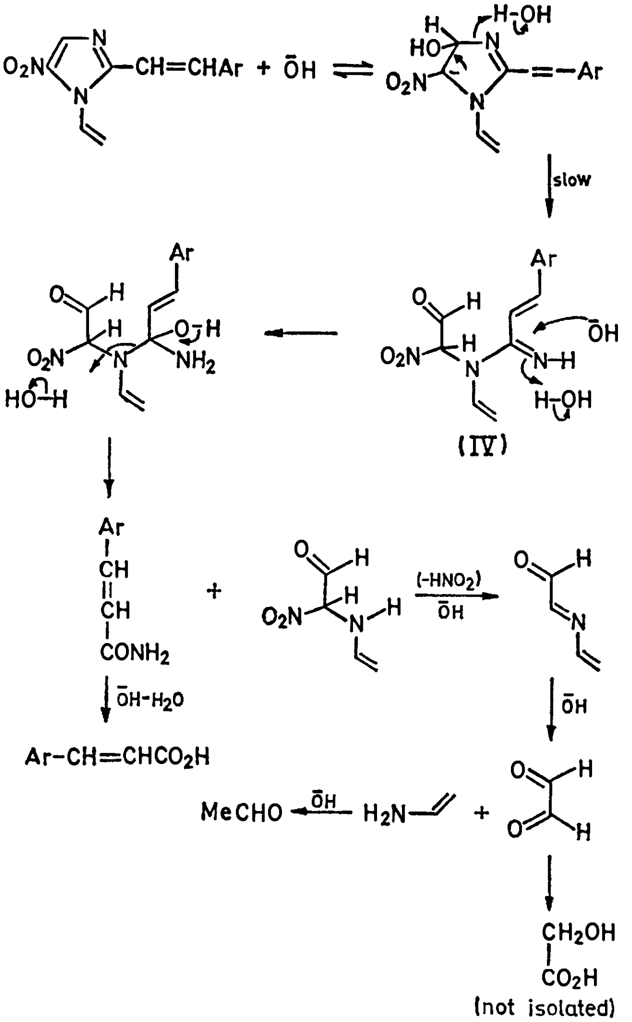
* In one experiment, 5-nitro-2-(*trans*-*m*-trifluoromethylstyryl)-N-vinylimidazole was treated with a small aliquot portion of aqueous tetramethylammonium hydroxide in dimethyl sulphoxide. On mixing the reactants a pink colour was apparent, which faded before a visible spectrum could be recorded. Coloured species have been reported in the reaction of 4-ethoxy-1,2-dimethyl-5-nitroimidazole with ethoxide.[4] The Meisenheimer structure (III) was suggested as the source of the colour.

[9] J. B. Conn, *Analyt. Chem.*, 1948, **20**, 585.

[10] Lilly Industries Ltd., *Chem. Abs.*, 1971, **74**, 53,790*s*.

coupling constants of the vinylic hydrogen atoms of 16 ± 1 Hz. The methyl and imidazole substituents were also *trans* to each other in the *N*-prop-2-enyl compound, the vinylic hydrogen coupling constant being 14 Hz.



SCHEME 3

4-*Carboxy*-trans-*cinnamic acid and its dimethyl ester.* 4-Carboxybenzaldehyde (4 g), malonic acid (2·8 g), pyridine (25 ml), and piperidine (few drops) were heated on a steam-bath for 5 h. 4-Carboxy-*trans*-cinnamic acid was isolated after dilution with water and acidification. It was converted into its dimethyl ester with BF_3 in methanol. The diester, after recrystallisation from methanol, had m.p. 125 °C (lit.,[11] 125·5—126·5 °C).

Solvents and bases. Dimethyl sulphoxide was purified by elution through Grade 5A molecular sieve followed by three distillations under reduced pressure from calcium hydride as described previously.[12] Sodium hydroxide solutions were prepared as required and titrated against standard acid. Tetramethylammonium hydroxide (B.D.H.) was used without further purification.

Reaction of the Acid (I) *with Aqueous Hydroxide.—Identification of solid products.* Compound (I) (200 mg) was shaken with aqueous sodium hydroxide solution (2N, 50 ml) for 2 h. The dark reaction mixture was acidified with excess of dilute hydrochloric acid and extracted with chloroform (3 × 25 ml). The chloroform extracts were dried ($MgSO_4$) and evaporated to give a light brown residue (135 mg, *i.e.* 97% based on 4-carboxy-*trans*-cinnamic acid). The residue was heated under reflux with BF_3–methanol (25 ml) for 1 h and the ester produced was extracted into ether and estimated by comparison with an authentic sample of the diester by g.l.c. on a Pye–Unicam 104 gas chromatograph. The chromatographic conditions were as follows; column, 3% JXR on Gas Chrom Q, 80—100 mesh, 5 ft; column temperature, 150 °C; carrier gas, N_2; flame ionisation detection. Control experiments showed that the recovery for the methylation process was 80% and the yield of 4-carboxy-*trans*-cinnamic acid from compound (I) was 85%. The g.l.c. study confirmed the absence of cinnamic, benzoic, or terephthalic acid among the hydrolysis products.

Volatile components. Compound (I) was decomposed in a closed reaction system under reduced pressure. As the reaction proceeded the evolved gases, which equalised the pressure, were collected in a flask, which was then sealed from the atmosphere by a serum cap. Samples of this gas showed g.l.c. peaks with the retention times of acetaldehyde and acetylene (column, Porapak R, 5 ft; column temperature, 150 °C; carrier gas N_2; flame ionisation detection). Mass-spectrometric analysis of the gases with an MS-902 mass spectrometer confirmed this assignment (acetaldehyde; accurate mass measurements for *m/e* 44, 43, and 29 in excellent agreement for C_2H_4O, C_2H_3O, and CHO, respectively; acetylene *m/e* 26 in excellent agreement for C_2H_2).

Kinetic Studies.—The rates of decomposition of the styrylimidazoles were monitored by following the decrease in absorbance of the reaction solution at 370 nm. The cinnamic acid product does not absorb in this region, and in the dilute solutions employed for the kinetic studies colouring effects do not arise from polymerisations. All reactions were carried out in 1 cm silica cells in the thermostatted cell compartment of a Unicam SP 700 spectrophotometer ($30 \pm 0{\cdot}1$ °C). To simplify kinetics, a large excess of base over substrate was always employed and all reactions exhibited good pseudo-first-order kinetic behaviour for at least 80% reaction. Rate coefficients were calculated from the slope of a graph of log $(D_t - D_\infty)$ against time where D_t is the absorbance at time *t* and D_∞ after at least 10 half-lives. The spectra of completely decomposed solutions were identical to those of the standard substituted *trans*-cinnamic acids in the two cases (4-carboxy- and unsubstituted acid) which were checked.

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[11] R. F. Heck, *J. Amer. Chem. Soc.*, 1968, **90**, 5518.

[12] A. F. Cockerill, *J. Chem. Soc.* (*B*), 1967, 964.