Potentially Bifunctional Reactants. Aromatic Nucleophilic Substitution by Imidazole or Pyrazole

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Quantitative *N*-2,4-dinitrophenylation of imidazole by 1-fluoro- (FDNB) or 1-chloro-2,4-dinitrobenzene (CDNB), or of pyrazole by FDNB occurs in benzene. The kinetics of the reaction of FDNB with imidazole are third-order overall (second-order with respect to imidazole) at low imidazole concentration, while levelling off of the rate occurs at higher imidazole concentration. Kinetics for the other reactions fit an equation containing terms both first- and second-order in the nucleophile. These results are interpreted in terms of an addition–elimination mechanism, with decomposition of the intermediate into products being fast for CDNB and slow (involving bifunctional reactivity for pyrazole and monofunctional reactivity for imidazole) for FDNB.

ANCHIMERIC assistance phenomena play a major role in a great variety of organic reactions.[1] Much interest has recently developed regarding substitution reactions by potentially tautomeric [2] bifunctional reagents, such as amidines. In this case the relative position of the attacking nitrogen atom and of the hydrogen atom (to be donated) on the other nitrogen atom may be such that they become concertedly involved in a cyclic transition state.[3a] Whether amidines do really behave in this way in the important (for its biological implications) case of esters has been disputed.[3b]

We have recently found strong evidence in favour of such bifunctional reactivity of amidines.[4] Briefly, by taking aromatic nucleophilic substitution as a model reaction, we have shown that bifunctional reactivity of benzamidine occurs in non-polar non-protic media only when catalysis of the removal of both a proton and the leaving group is needed as in the case of 4-fluoro-1,6-dinitronaphthalene (FDNN). When, however, both the leaving group and a proton are lost in a fast step as in the case of 1-chloro-2,4-dinitrobenzene (CDNB), the transition state of the benzamidine reaction is not par-particularly stabilised with respect to that of an amine of comparable basicity, such as n-butylamine.

We have now extended this work to another potentially bifunctional protic nucleophile, pyrazole. As a model reaction we have again chosen aromatic nucleophilic substitution of 1-fluoro-2,4-dinitrobenzene (FDNB) in benzene. Here, both base catalysis of the proton transfer and acid catalysis of the removal of fluoride ion are expected.[5] Molecular models show that in the case of a tautomeric reagent like pyrazole this can occur in a concerted manner *via* a cyclic transition state.

We have also studied the reactions of imidazole with FDNB or CDNB since molecular models indicate that the two functionalities of imidazole are too far apart to be able to take part in a concerted manner in the reaction. Therefore, monofunctional reactivity is expected even with the fluoro-compound in this case.

The comparison of the mechanism of the pyrazole and the imidazole reactions was suggested in part by the recognised catalytic role of the imidazole residue in many important biological reactions.

Moreover, even with regard to nucleophilic aromatic substitution, the relative reactivity towards FDNB or CDNB of the amino- and the imidazole function in both L-histidine [6] and histamine [7] have aroused considerable interest. Also, nucleophilic aromatic substitution is currently used to arylate both imidazole and pyrazole or their derivatives.[8] Therefore, even in this restricted respect, there is some interest in studying in detail the mechanism of aromatic substitution by imidazole and pyrazole as nucleophiles.

RESULTS

Quantitative substitution of either fluorine or chlorine by imidazole, and of fluorine by pyrazole was observed in all cases reported here in the absence of light (the end products of these reactions, particularly *N*-2,4-dinitrophenylimidazole, are known to be quite light sensitive [9]).

Irradiation with a 300 W tungsten lamp through Pyrex glass of a stirred nitrogen-flushed dilute solution (0·08 g l^{-1}) of *N*-2,4-dinitrophenylimidazole in anhydrous benzene at room temperature gave rapid precipitation in good yield of yellow crystals, m.p. 143—148°. This material is insoluble in most solvents except carbitol, dimethylformamide, dimethyl sulphoxide, and pyridine and we were unable to recrystallise it. T.l.c. showed a single spot. No peak likely to be the molecular ion was visible in the electron-impact mass spectrum which indicated the material to be polymeric. The u.v. absorption spectrum in carbitol was different from the starting material showing two strong absorption bands at 308 and 260 nm. ^{1}H N.m.r. spectroscopy in hexadeuteriodimethyl sulphoxide showed a complex series of peaks at δ 6·5—9·0 p.p.m. (relative integration 0·86) and a broad band (1·0) which disappeared on the shaking with D_2O. Photolysis at higher concentrations, under otherwise identical conditions, gave identical results. Under these conditions, irradiation of *N*-2,4-dinitrophenylpyrazole gave only intractable tars. This investigation was not further pursued and low temperature photolysis was not attempted.

[1] B. Capon, *Quart. Rev.*, 1964, **18**, 45.
[2] P. R. Rony, *J. Amer. Chem. Soc.*, 1969, **91**, 6090.
[3] (*a*) F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 3081; (*b*) H. Anderson, C. Su, and J. W. Watson, *ibid.*, 1969, **91**, 482.
[4] G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1971, 2811; *J.C.S. Perkin II*, 1972, 188.
[5] F. Pietra, *Quart. Rev.*, 1969, **23**, 504.
[6] L. C. Craig and W. Konigsberg, *J. Org. Chem.*, 1957, **22**, 1345; and previous paper by other authors referred to therein.
[7] D. A. Nelson, Abstracts of Papers, 158th A.C.S. meeting, 1969, ORGN 52.
[8] See, for example, H. Reimlinger and J. F. M. Oth, *Chem. Ber.*, 1964, **97**, 331; J. Elguero, A. Fruchier, and R. Jacquier, *Bull. Soc. chim. France*, 1967, 2619; M. D. Coburn and P. N. Neuman, *J. Heterocyclic Chem.*, 1970, **7**, 1391.
[9] J. F. K. Wilshire, *Austral. J. Chem.*, 1966, **19**, 1935.

The rate data for the reactions of imidazole (IM) with CDNB or FDNB in benzene are collected in Table 1, A and B and, for easier appreciation, in Figures 1 and 2. The

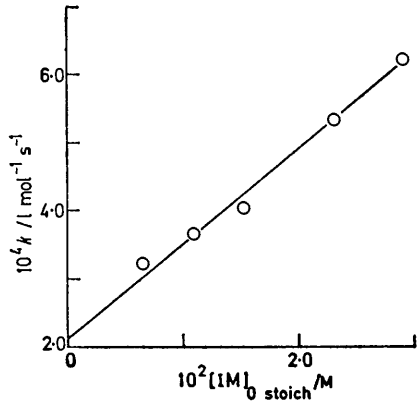


FIGURE 1 Reaction of imidazole (IM) with 1-chloro-2,4-dinitrobenzene (CDNB) in benzene at 100°. Plot of the second-order rate coefficient (k = rate/[CDNB][IM]) against imidazole concentration

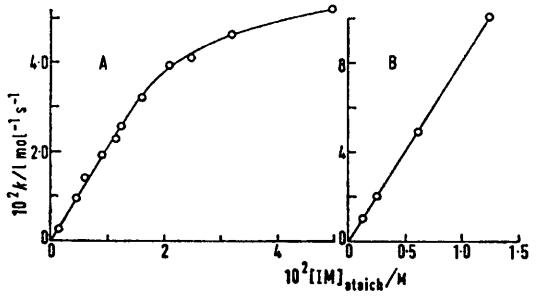


FIGURE 2 Reaction of imidazole (IM) with 1-fluoro-2,4-dinitrobenzene (FDNB) in benzene A, at 25° and B, at 100°. Plot of the second-order rate coefficient (k = rate/[FDNB][IM]) against imidazole concentration

data for the CDNB reaction fit equation (1; X = Cl) with both k_0 and k_{IM} terms being of sizable magnitude (Table 2).

$$k = \text{Rate}/(\text{ArX})[\text{IM}] = k_0 + k_{IM}[\text{IM}] \quad (1)$$

In the case of FDNB, equation (1; X = F), where the k_0 term has a negligible magnitude (Figure 2 and Table 2) holds only up to [IM] *ca.* $1{\cdot}2 \times 10^{-2}$M. On further increasing the imidazole concentration, k increases in a less than linear fashion (Figure 2A). The reaction of FDNB with imidazole has also been examined in benzene at 100°. Data of Table 2,B show that equation (1) (with $k_0 = 0$ within the limits of the experimental error) holds up to [IM] = $1{\cdot}24 \times 10^{-2}$M. This is better appreciated from Figure 2B. The rate of the reaction of FDNB with imidazole is increased by added quinuclidine (QUIN) (Table 1,C).

TABLE 1

Second-order rate coefficient (k = Rate/[ArX][IM]) for the reactions of imidazole (IM) with A, 1-chloro-2,4-dinitrobenzene; B, 1-fluoro-2,4-dinitrobenzene; and C, 1-fluoro-2,4-dinitrobenzene in the presence of quinuclidine (QUIN), in benzene

A 1-Chloro-2,4-dinitrobenzene (initial conc. $5{\cdot}0 \times 10^{-4}$M); temp. 100·0 °C

10^2[IM]/M	0·657	1·12	1·52	2·30	2·92
10^4k/l mol^{-1} s^{-1}	3·21	3·60	4·01	5·13	6·21

B 1-Fluoro-2,4-dinitrobenzene (initial concn. $4{\cdot}5 \times 10^{-5}$M); temp. 25·0 °C, unless otherwise stated

10^2[IM]/M	0·124	0·125 [a]	0·248 [a]	0·455	0·609
10^2k/l mol^{-1} s^{-1}	0·270	1·01	2·01	0·940	1·39
10^2[IM]/M	0·620 [a]	0·911	1·15	1·24 [a]	1·24
10^2k/ mol^{-1} s^{-1}	4·90	1·92	2·36	10·1	2·57
10^2[IM]/M	1·62	2·10	2·48	3·20	4·98 [b]
10^2k/l mol^{-1} s^{-1}	3·19	3·93	4·10	4·61	5·17

C 1-Fluoro-2,4-dinitrobenzene (initial concn. $4{\cdot}5 \times 10^{-5}$M) with added quinuclidine (QUIN).[c] Initial concn. of imidazole $9{\cdot}94 \times 10^{-3}$M; temp. 25·0 °C

10[QUIN]/M		0·322	0·645	1·29	4·19
10^2k/l mol^{-1} s^{-1}	2·04	5·38	8·06	10·1	17·2

[a] At 100°. [b] Suprasaturated. However, no precipitation was observed during the experiment. [c] Under these conditions, quinuclidine does not compete effectively with imidazole for replacement of fluorine (see text).

Figure 3 shows that equation (2) is not obeyed, the increase

$$k = \text{Rate}/[\text{FDND}][\text{IM}] = k_0 + k_{IM}[\text{IM}] + k_{QUIN}[\text{QUIN}] \quad (2)$$

of k with [QUIN] being less than linear in the whole concentration range of quinuclidine. However, an estimate of k_{QUIN} may be obtained through equation (2) from the slope at [QUIN] = 0 (Figure 3 and Table 2).

The kinetics for the reaction of FDNB with pyrazole (PYR) obey equation (3), with k_0 and k_{PYR} both being important.

$$k = \text{Rate}/[\text{FDNB}][\text{PYR}] = k_0 + k_{PYR}[\text{PYR}] \quad (3)$$

TABLE 2

Reaction (Table 1) of 1-chloro-2,4-dinitrobenzene (A) or 1-fluoro-2,4-dinitrobenzene (B), (C) with imidazole (IM) in benzene in the presence or not of quinuclidine (QUIN). Treatment of the data (Table 1) according to the equation k = rate/[ArX][IM] = $k_0 + k_{IM}$[IM] + k_{QUIN}[QUIN]

Data of Table 1	t/°C	10^4k_0 / l mol^{-1} s^{-1}	10^2k / l^2 mol^{-1} s^{-1}	k_{QUIN} / l^2 mol^{-2} s^{-1}	k_{IM}/k_0 / l mol^{-1}	k_{QUIN}/k_0 / l mol^{-1}
A	100·0	2·1	1·4		66·7	
B, C	25·0	*ca.* 0	213 [a]	1·13 [b]	Very large	Very large

[a] The data fit the above equation only up to *ca.* $1{\cdot}1 \times 10^{-2}$M-imidazole. For higher concentrations of imidazole k increases less than linearly (Figure 2A). [b] In the range of quinuclidine concentrations investigated, k increases less than linearly with quinuclidine concentration (Figure 3); the slope refers to zero quinuclidine concentration.

DISCUSSION

We show that the rate data for imidazole obtained favour the addition–elimination mechanism of the Scheme (which, in its general aspect, is well supported for reactions with a number of other nucleophiles [5])

with imidazole reacting through its tertiary nitrogen atom (where B represents a base).

In the case of CDNB the kinetic law [equation (1)] contains both a first- and a second-order term in imidazole. The value of the ratio between the second- and

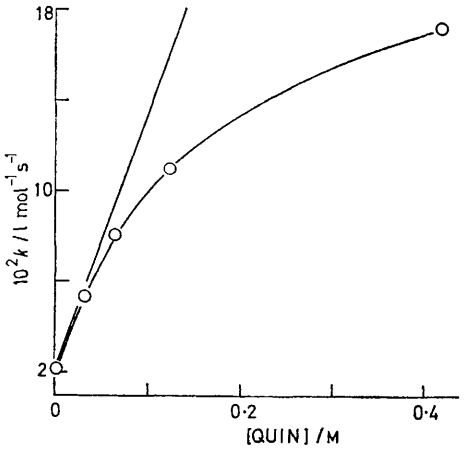
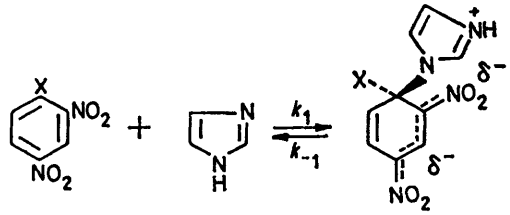
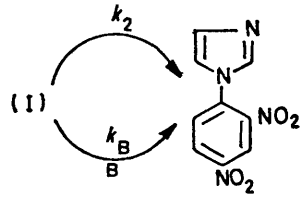


FIGURE 3 Reaction of imidazole (IM) ($9{\cdot}94 \times 10^{-3}$M) with 1-fluoro-2,4-dinitrobenzene (FDNB) in benzene with added quinuclidine (QUIN). Plot of the second-order rate coefficient (k = rate/[FDNB][IM]) for formation of *N*-2,4-dinitrophenylimidazole against quinuclidine concentration

the first-order term, *ca.* 67 mol^{-1} l (Table 2), is markedly higher than those found for the reactions of primary or secondary amines with the same substrate (where typical values of less than unity [10] or of *ca.* 7 [11] have been observed for amines of very high or of very low reactivity,



(I)



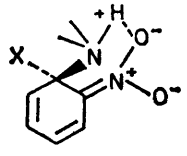
SCHEME

respectively). This could suggest that, unlike the case of amines,[12] decomposition into products of the intermediate (I; X = Cl) is rate-limiting, thus requiring general base catalysis or, which is kinetically equivalent, general acid catalysis of the conjugate base of (I).

However, this deviation from the first-order behaviour with respect to imidazole appears to be modest indeed when the corresponding reaction of FDNB in examined. Here, in fact, clean second-order kinetics with respect to imidazole, or, in other words, a value of the k_{IM}/k_0 ratio which tends to infinity, have been obtained. This clearly fits into the steady-state equation (4) of the mechanism of the Scheme, with $k_{-1} \gg k_2 + k_B[B]$.*

$$k = (k_1k_2 + k_1k_B[B])/(k_{-1} + k_2 + k_B[B]) \quad (4)$$

Moreover, the negligible magnitude of the k_0 term of equation (2) indicates that imidazole attacks the aromatic carbon through its tertiary nitrogen atom. In fact, were the secondary nitrogen the nucleophilic atom, the interaction between the ammonium hydrogen atom and the *o*-NO_2 group in the transition state should displace decomposition of the intermediate towards products (*i.e.* a substantial k_0 term should result). This is in fact the case of the substitution of fluorine from fluoro-aromatics with an *o*-NO_2 group by primary or secondary amines where the ammonium proton is available to the *o*-NO_2 group,[10,13] as indicated by structure (II).



(II)

In the case of CNDB the addition–elimination mechanism of the Scheme may be retained for analogy with the above case of FDNB and all other cases where there is evidence for an intermediate along the reaction pathway.[5] However, the modest deviation from the first-order behaviour with respect to imidazole, in the absence of a detailed study of the influence of added bases of various base strength, cannot be interpreted as base catalysis of the breakdown of intermediate (I; X = Cl). Rather, rate acceleration by added imidazole can be interpreted here as a stabilisation of the transition state by a common solvent effect or by a more specific effect of unclear origin. That such effects are more pronounced for reactions of imidazole than for reactions of primary or secondary amines is in line with a structure of the transition state which resembles [14] (I; X = Cl) in the former case and (II; X = Cl) in the latter one. The intermediate (I) should, in fact, be more susceptible to external influences (such as solvation effects, *etc.*) than (II) where the positive charge on the ammonium proton and the nega-

* Here the problem of whether intermediates of type (I) or their conjugate bases represent the predominant form of the intermediate [5] is not discussed as it is immaterial for the conclusions to be drawn from this work.

[10] F. Pietra and F. Del Cima, *Tetrahedron Letters*, 1967, 4573.
[11] C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 2570.
[12] See, however, footnote on p. 1598 in F. Pietra, D. Vitali, and S. Frediani, *J. Chem. Soc.* (*B*), 1968, 1595.
[13] F. Pietra and F. Del Cima, *Tetrahedron Letters*, 1970, 1041.
[14] G. Biggi and F. Pietra, *J. Chem. Soc.* (*B*), 1971, 44.

tive charge on the *o*-NO_2 group oxygen may compensate each other internally.

Therefore, under the proviso made above,[12] we do not favour the interpretation[15] of the reaction of picryl chloride with imidazole, in chloroform, in terms of a mechanism similar to that of the Scheme with base catalysis of the breakdown of the intermediate into products. Rather, we prefer an interpretation similar to that above for the case of CDNB.

We have thus far only considered the linear portion of Figure 2A for the reaction of FDNB with imidazole. If

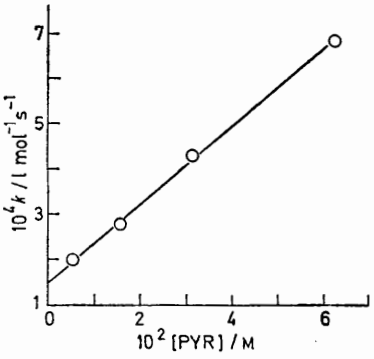


FIGURE 4 Reaction of pyrazole (PYR) with 1-fluoro-2,4-dinitrobenzene in benzene. Plot of the second-order rate coefficient (k = rate/[FDNB][PYR]) against pyrazole concentration

the whole plot is examined, the levelling off of the rate which occurs on raising imidazole concentration above *ca.* 1×10^{-2}M might suggest that there is a change in the rate-limiting step with imidazole concentration. The change would be from rate-limiting decomposition of (I; X = F) into products at low imidazole concentration to rate-determining formation of (I; X = F) at high imidazole concentration.[5] Also, the kinetic effect of an added base such as quinuclidine seems to be qualitatively in line with this (Figure 3). However, it must be noted that in the case of imidazole the rate levels off at a much lower value than in the case of quinuclidine, while according to the mechanism of the Scheme a levelling off of the rate towards the same value [k_1, as is immediately clear from examination of equation (4)] should be expected.

Therefore, either the mechanism of the Scheme has to be modified to take into account base catalysis of the k_1 step, or activity coefficient effects are responsible for the levelling off of the rate. We prefer the second view as there is no precedent, thus far, for the first alternative in aromatic substitution by amines.[5] In other words, the levelling off of the rate in the reaction of FDNB with imidazole might be attributed to association phenomena among reactants and catalysts.[16] The absence of such phenomena in the other reactions studied here might be attributed to the reaction temperature being 75° higher than in the case of FDNB with imidazole. In any case, this point is of secondary importance with respect to the main conclusions which can be drawn from this work.

Table 3 and Figure 4 show that the kinetic data for the reaction of FDNB with pyrazole are very similar to those obtained for the reaction of CDNB with imidazole.

TABLE 3

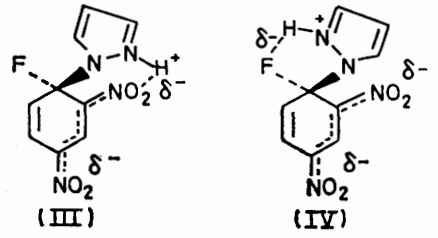
A second-order rate coefficient (k = Rate/[ArX][PYR]) for the reaction of pyrazole (PYR) with 1-fluoro-2,4-dinitrobenzene in benzene at 100·0 °C (initial concentration of fluoro-compound $6{\cdot}0 \times 10^{-4}$M)

10^2[PYR]/M	0·55	1·57	3·14	6·26
$10^4 k$/l mol^{-1} s^{-1}	1·98	2·78	4·28	6·83

B Treatment of the data of Table 3, A according to the equation (see Figure 4) k = Rate/[ArX][PYR] = $k_0 + k_{PYR}$[PYR]

$10^4 k_0$ / l mol^{-1} s^{-1}	$10^3 k_{PYR}$ / l^2 mol^{-2} s^{-1}	k_{PYR}/k_0 / l mol^{-1}
1·50	8·70	58·0

In fact, a rate acceleration by the nucleophile (k_{PYR}/k_0 = 58·0 mol^{-1} l) is observed which is extremely modest when compared to that for the reaction of FDNB with imidazole. If a mechanism of the form shown in the Scheme is retained, these observations can only be explained in terms of a favourable decomposition of the intermediate for the pyrazole reaction towards products, owing to the intramolecular stabilisation of positive and negative charges shown in (III) or (IV), or, statistically, to both.



Molecular models clearly show that the acidic proton may be at a bonding distance with respect to an oxygen atom of the *o*-NO_2 group in conformation (III), whereas, contrary to the case of benzamidine,[4] the H · · · F distance in conformation (IV) is far greater than a bonding one. Therefore, the predominant conformation of the transition state should be best represented by structure (III).

This is clearly the only reasonable rationalisation of the much more favourable ' spontaneous ' decomposition of the intermediate towards products in the case of pyrazole [(III)] than of imidazole [(I; X = F)]. In fact, without advocating the specific effect discussed above, the addition intermediate would preferably decompose towards reagents in the case of pyrazole, rather than of imidazole, owing to the much lower basicity (and therefore nucleophilicity; we do not consider possible α-effects as they seem to be nearly negligible with nitrogen nucleophiles in aromatic substitution[14]) of the former with respect to the latter.

Clearly a mechanistically significant comparison of the reaction rates can only be made through the k_0 terms and

[15] R. Minetti and A. Bruylants, *Bull. Acad. royale de Belgique (Classe des Sciences)*, 1970, 1047.
[16] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1200.

pyrazole prevails. At higher nucleophile concentration we can only compare overall rates and the much greater basicity of imidazole over pyrazole (by *ca.* 4·5 pK units in water [17]) favours the first over the second.

Finally, we would like to emphasise that bifunctional reactivity is not a property associated with nucleophile structure but with transition state structure. Therefore, different reactions than those studied here could well show a different pattern of reactivity towards imidazole and pyrazole.

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage apparatus and are uncorrected. U.v. spectra were taken on a Beckmann DU or a Unicam SP 800 spectrophotometer with 10 mm stoppered quartz cuvettes.

Materials.—Benzene was purified as before.[18] Imidazole was recrystallised several times from benzene and then sublimed under vacuum, m.p. 88—89°. Pyrazole was recrystallised several times from cyclohexane and then fractionally sublimed under vacuum. The fraction with m.p. 66·5—67·5° was used for the kinetics. *N*-2,4-dinitrophenyl-imidazole and -pyrazole were prepared according to the literature [9] and were stored under nitrogen in the dark and manipulated under nitrogen under red light. No appreciable decomposition of these compounds was observed under our reaction conditions. Quinuclidine was sublimed and handled under nitrogen.

Kinetics.—The kinetics were determined by following the increase of the u.v. absorption of *N*-2,4-dinitrophenyl-pyrazole or of -imidazole. In the first case the wavelength, 312 nm, corresponding to the absorption maximum (ε *ca.* 12,000 l mol^{-1} cm^{-1}) was selected. In the other case, where there is no absorption maximum in the spectral region available for examination in benzene solution, the kinetics were followed at 325 nm (ε *ca.* 3750 l mol^{-1} cm^{-1}). In both cases the Lambert–Beer law is strictly followed in the concentration ranges used for the u.v. analysis. In any case, the u.v. absorption of the reaction mixture, after the appropriate number of half-lives, agreed well with that of the expected products.

The kinetics for the reaction of imidazole with FDNB, with or without added quinuclidine, were directly followed in a cuvette placed into the thermostatted container of the spectrophotometer. In all other cases the sealed ampoule technique (dilution with benzene, when necessary, before u.v. analysis) was utilised.

Financial support from C.N.R., Roma, is acknowledged. We thank also Dr. D. Vitali for preliminary experiments.

[1/1245 *Received*, 21*st July*, 1971]

[17] R. M. Acheson, 'An Introduction to the Chemistry of Heterocyclic Compounds,' Interscience, New York, 1967, p. 261.
[18] F. Pietra and F. Del Cima, *J. Org. Chem.*, 1968, **33**, 1411.