Formation and Thermal Reaction of *O*-(*N*-Acetylbenzimidoyl)benzamidoxime: Comparison with the Formation of 3,5-Disubstituted 1,2,4-Oxadiazoles from *O*-Acetylarylamidoximes and *O*-Aroylacetamidoximes

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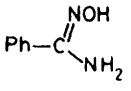
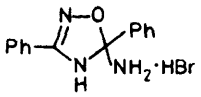
Salts of *O*-(benzimidoyl)benzamidoxime have been obtained by the action of *N*-chloro- or *N*-bromo-succinimide, or the halogens, on benzamidoxime. Acetylation of the free base gave the title compound, which underwent a thermal cyclisation, with loss of acetamide, to give 3,5-diphenyl-1,2,4-oxadiazole. The mechanism of this reaction, in diphenyl ether, closely paralleled the thermal cyclisation of *O*-acetylarylamidoximes and *O*-aroylacetamidoximes, and is thought to involve a polar cyclisation step followed by rate-determining proton transfer. ^{13}C N.m.r. spectra for 32 oxime, amidoxime, and oxadiazole derivatives are recorded, and substituent chemical shifts for the oxime, amidoxime, *O*-acetylamidoxime, 5-methyl-1,2,4-oxadiazol-3-yl, and 3-methyl-1,2,4-oxadiazol-5-yl groups on the phenyl ring are calculated.

In continuation of studies [1] on the reactions of oximes with *N*-chlorosuccinimide and sulphides in the presence of triethylamine (Corey oxidation conditions [2]) we found that benzamidoxime (1), when treated with *N*-chlorosuccinimide alone gave the hydrochloride of a base, $C_{14}H_{13}N_3O$. The hydrobromide was obtained in like fashion using *N*-bromosuccinimide, and also from reaction with bromine. Treatment of the salts with triethylamine gave the free base.

The same base was first reported by Stieglitz [3] in 1889, who obtained it from reaction between benzamidoxime and an alkaline solution of potassium ferricyanide, or a solution of benzenediazonium salts. He subsequently prepared the hydrochloride from the base. Krümmel [4] later obtained the two salts from reaction between benzamidoxime and chlorine or bromine, and proposed structure (2) for the hydrobromide. These results have been included in a review,[5] without comment, but have not otherwise been considered in the intervening 90 years.



(1)



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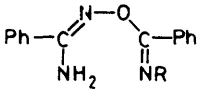


(3)

a; R = H
b; R = $COCH_3$

From the chemical properties of the base and salts reported earlier (which we confirm) and from their spectroscopic characteristics, we find the base to have the tautomeric open-chain structure (3a). The main new chemical evidence is the formation of a monoacetyl derivative (3b), which, on being heated, gave 3,5-diphenyl-1,2,4-oxadiazole (4) [6] and acetamide. This reaction is discussed in detail below. These chemical properties are included in the summarising Scheme 1.

^1H N.m.r spectroscopy gave little information concerning the salts, but the base clearly showed two phenyl rings both with deshielded *ortho*-protons, and the same was true for the acetyl derivative (3b). ^{13}C N.m.r. spectroscopy demonstrated that the base (3a) (δ_C 156.0 and 162.0 p.p.m.) and the monoacetyl compound (3b) (δ_C 156.0 and 148.2 p.p.m.) both had two C=N groups, one of the benzamidoxime type (benzamidoxime, δ_C 151.4 p.p.m.), and one affected by acetylation. The electron-impact mass spectrum of base (3a) (which gave an $M+1$ ion in the field-desorption mode) closely resembled that of the oxadiazole (4), and the electron-impact mass spectrum of the hydrochloride matched that of benzamidoxime. This salt gave no molecular ion in the field-desorption mode.

Whilst the ^1H n.m.r. spectrum of the acetyl derivative (3b) clearly showed two NH protons in one signal (D_2O exchangeable), it was necessary to demonstrate whether there was one NH_2 group or two NH groups present, so that possible tautomeric structures might be excluded. The acetyl compound (3b) was partially, and then fully, deuteriated on nitrogen, when comparison of the N–H and N–D stretching frequencies in the i.r. (Table 1) of the undeuteriated, partially deuteriated, and deuteriated samples demonstrated that indeed a single NH_2 was present in compound (3b). This technique has been used,[7] *inter alia*,[8] to show that benzamidoxime has the amino-oxime form (1) and not the imino-hydroxylamine form.

TABLE 1

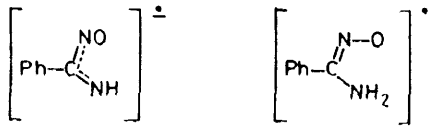
I.r. N–H and N–D stretching frequencies (cm^{-1}) for monoacetyl derivative (3b) *etc.* in chloroform solutions

	N–H (str.)		N–D (str.)	
$PhC(NH_2)=NOC(Ph)=NAc$	3 525	3 425		
$PhC(NHD)=NOC(Ph)=NAc$ [a]	3 475		2 565	
$PhC(ND_2)=NOC(Ph)=NAc$			2 635	2 495

[a] Also weak bands due to NH_2 and ND_2 contaminants.

A comparison of the u.v. spectra of the base (3a), its hydrochloride, and the acetyl derivative (3b) [$\lambda_{max.}$ 226, 260(sh); 238, 275; 237, 265(sh) nm, respectively] showed their close structural relationship, the shorter wavelength maxima corresponding to the benzimidoyl chromophore [PhC(OR)=NH, $\lambda_{max.}$ 228 nm] and the longer wavelength maxima to the benzamidoxime chomophore [$PhC(NH_2)$=NOH, $\lambda_{max.}$ 260 nm]. The base and its hydrochloride gave identical u.v. spectra in ethanol–acid solutions and again in ethanol–alkali solutions.

The mechanism by which the salts of base (3a) were formed is not known. It is known, however, that oxidation of benzamidoxime with alkaline potassium ferricyanide gives the radical anion (5a),[9] and although this reference quotes no products of reaction, Stieglitz [3] reported a moderate yield of base (3a) from a similar reaction. It is likely that halogen radicals react with benzamidoxime to give the radical (5b), which adds to a second molecule of benzamidoxime. Subsequent hydrogen abstraction and loss of hydroxylamine would give base (3a).

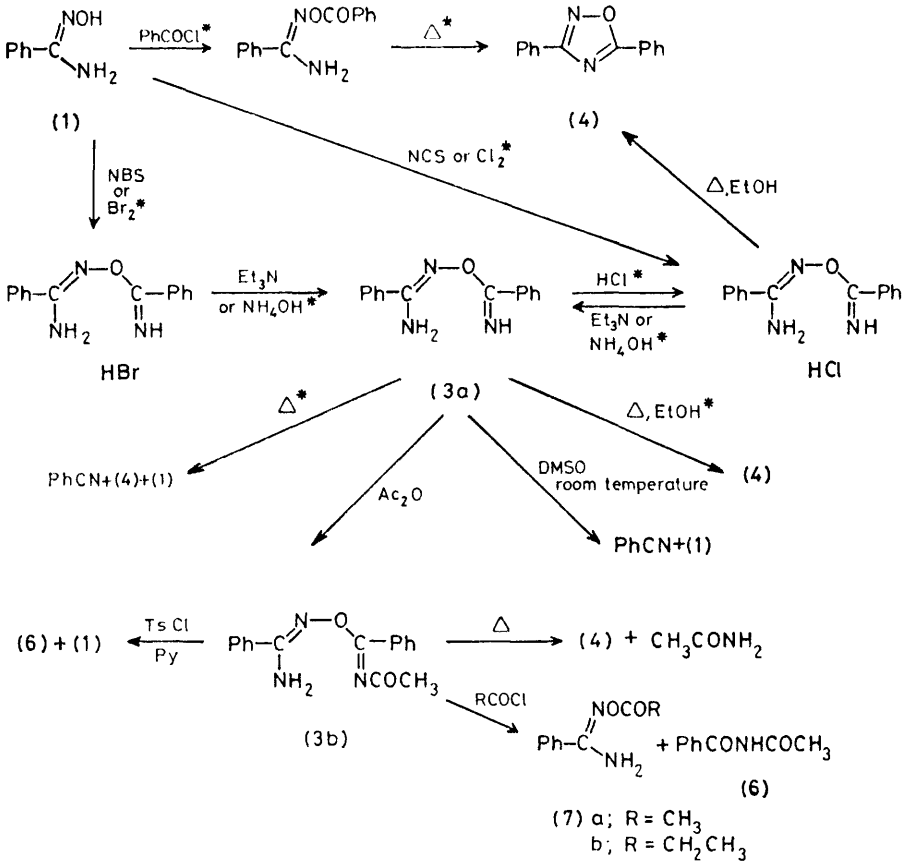


(5a) (5b)

with propionyl chloride gave products (6) and (7b). A mechanism, regarded as tentative since it requires the salt (8) to precipitate out of solution rather than simply lose a proton, is shown in Scheme 2. Toluene-*p*-sulphonyl chloride in pyridine at room temperature converted the monoacetyl derivative (3b) into *N*-acetylbenzamide (6) and benzamidoxime (1), for which a similar mechanism may be written (Scheme 3) involving intermolecular nucleophilic attack by solvent, rather than neighbouring-group participation by a carbonyl group.

The observation that the acetyl derivative (3b) was cleanly converted into 3,5-diphenyl-1,2,4-oxadiazole (4) and acetamide when it was heated in solution prompted an investigation into the mechanism of this reaction, outlined in equation (i).

It should be pointed out at this stage that the stereochemistry about the imidoyl carbon–nitrogen double bond is not known, but isomerisation about this bond

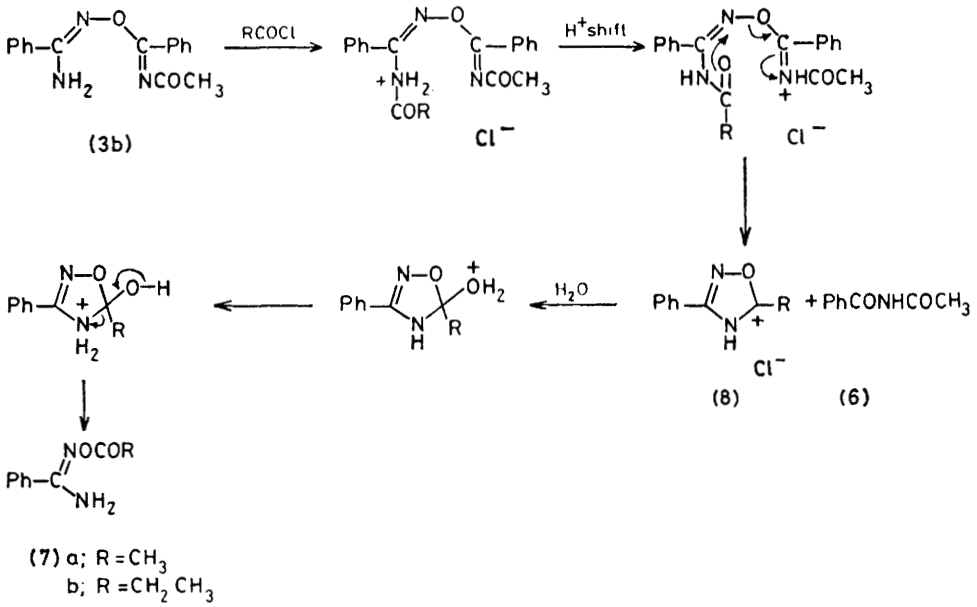


SCHEME 1 Summary of reactions reported in this paper and (*) by other authors [3,4]

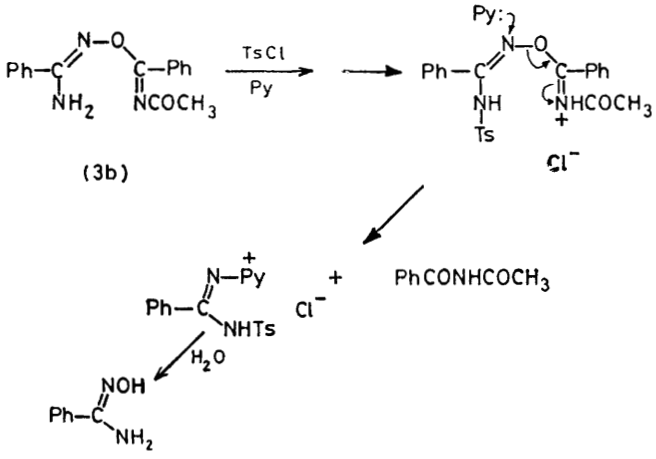
Attempts to acylate further the monoacetyl derivative (3b) gave interesting results. Compound (3b) was treated with acetyl chloride in the presence of magnesium sulphate and sodium carbonate to keep the ethereal solution dry and free of hydrogen chloride. After reaction, the solution contained *N*-acetylbenzamide (6), while the filtered solid, when treated with water–ether gave *O*-acetylbenzamidoxime (7a). A similar reaction may safely be assumed to be fast [10] at the temperatures used for cyclisation (and well below them), and so this point is not of mechanistic significance. The rate of the reaction in equation (i) was followed, by n.m.r. spectroscopy, at a number of temperatures in diphenyl ether, and in a number of solvents. The results are given in Tables 2 and 3. First-order kinetics were observed in every case. In no experiments were signals attribut-

able to intermediates to be seen. Attempts to use protic solvents (alcohols) led to complex mixtures of products.

Compound (3b) dideuteriated on nitrogen (95% by n.m.r.) was also studied. At 110.2°, the rate constant for compound (3b) was 6.5×10^{-4} s^{-1} while that for its dideuterio-analogue was 4.33×10^{-4} s^{-1} giving, after correction for isotopic content, a primary kinetic isotope effect of 1.54. A secondary kinetic isotope effect for an NH_2 group compared to an ND_2 group acting as a nucleophile [11] is <1. It is clear that adventitious water present in the kinetic solutions might exchange with the deuteriated compound, thereby giving an experimental value for k_H/k_D lower than the true one. Investigation of the ^1H content of the product acetamide (which should reflect the overall isotope ratio present) was not feasible by ^1H n.m.r., and calculation of the isotope ratio from the intensities of the M, $M+1$, and $M+2$ peaks in the electron-impact mass spectrum (it gave a result of 50% ^2H, leading to a calculated k_H/k_D value of 3.01) could not be taken as a true measure, because of isotopic exchange in the mass spectrometer. This was demonstrated separately to be *ca.* 27% of ^2H label, but this was not a reproducible measurement. We subsequently obtained evidence that in dimethyl sulphoxide at least, exchange between ^2H-labelled compound (3b) and ^1H_2O (1 mole per mole) occurred at a similar rate to that of the cyclisation. Thus the true value for k_H/k_D is probably a little greater than 1.54 and certainly less than 3.01.

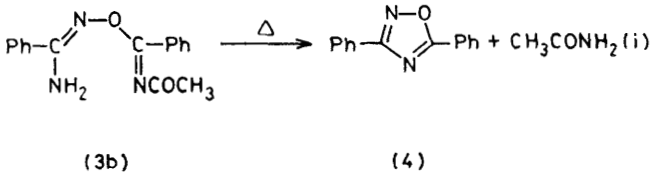


SCHEME 2 Mechanism for reaction of derivative (3b) with acyl chlorides



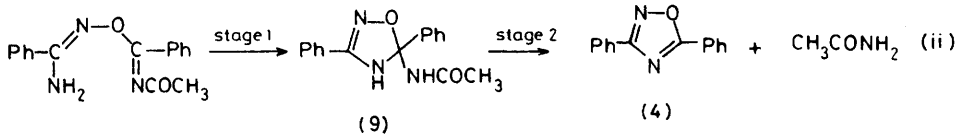
SCHEME 3 Mechanism for reaction of derivative (3b) with toluene-*p*-sulphonyl chloride in pyridine

The mechanism for this cyclisation may, from the structures of reactant and products, be outlined as in equation (ii), involving an intermediate (9) which is the acetyl derivative of the structure suggested in 1895.[4] The evidence so far accumulated (negative $\Delta S^{\ddagger}$, kinetic isotope effect >1.5, negligible solvent effect) would lead to the suggestion that the slow step is stage 2 of equation



(ii), with the first stage being reversible with the equilibrium lying far to the left (no intermediate seen). However, arguing against this is the observation that treatment of compound (3b) with sodium hydride in various solvents (THF, $CDCl_3$, C_5D_5N; reaction followed by n.m.r.) gave the same two products, without observable intermediates, quickly at room temperature and

below. This result suggests that the anion of compound (3b) was formed, it cyclised rapidly, and loss of acetamide followed quickly upon this, as in equation (iii). Therefore, if loss of acetamide, presumably a retro-ene reaction, was fast at normal temperatures, it could not be the slow step for the purely thermal reaction of equation (i). We thus retreat to considering stage 1 of equation (ii) being rate determining, and see two reasonable possibilities: (a) the stage involves a concerted addition of an N–H bond across the 1,4-termini of a heterodiene system (10), followed by fast tautomerism and retro-ene elimination [equation (iv)] or (b) the addition is a polar process (12) ⟶ (13) with rate-determining proton transfer [equation (v)].



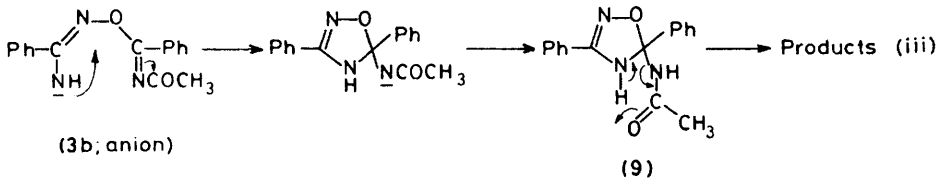


TABLE 2

Kinetic results for reaction of compound (3b) in diphenyl ether [a]

Temp. (°C)	10^5k/s^{-1}	Average $t_{\frac{1}{2}}$/min	
80.1	3.70, 3.78	309	
95.1	16.5, 15.5	72	
110.2	64.6, 65.4	18	E_a 25.1 ± 0.2 kcal mol^{-1}
122.4	171, 168	6.9	$\Delta S^{\ddagger}$ −10.0 ± 0.5 cal K^{-1} mol^{-1} (at 102°)

[a] Oil bath; see Experimental section.

Although equation (iv) shows a $[_\sigma 2_s + _\pi 4_s]$ process (10) ⟶ (11), it could also be written as a homo-[1,5]-hydrogen shift, or as using the lone pair of electrons on nitrogen in an eight-electron, anti-Hückel, aromatic transition state,[12] with phase dislocation (cruciconjugation) at nitrogen.[13] Inspection of Dreiding models suggests that some conformations of compound (3b) would allow reaction by any of these pathways. The problem thus resolved itself into determining whether ionic intermediates were involved in the reaction.

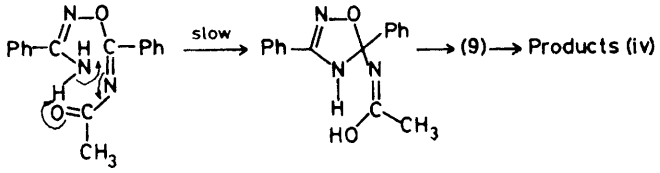
TABLE 3

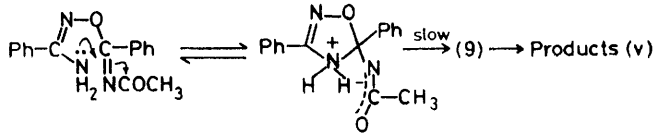
Rate constants at 110° for reaction of compound (3b) [a]

Solvent	Dielectric constant	Average k/s^{-1}	$t_{\frac{1}{2}}$/min
Diphenyl ether	3.65	5.9×10^{-4}	19.6
Nitrobenzene	34.8	6.0×10^{-4}	19.3
[$^2H_6$]Dimethyl sulphoxide	46.7	8.9×10^{-4}	13.0
Ethylene carbonate	89.6	6.1×10^{-4}	18.9

[a] Variable temperature probe; see Experimental section.

The *p*,*p*′-dimethoxy-analogue of compound (3b) reacted a little more slowly than compound (3b) itself (k 5.2 × 10^{-4} s^{-1} compared with 5.9 × 10^{-4} s^{-1} at 110° in diphenyl ether in the variable temperature probe of the n.m.r. spectrometer), but this symmetrically substituted compound may not be expected to show much change in rate even for an ionic reaction, since one substituted phenyl ring would be attached to the nucleophilic part of the molecule and the other to the electrophilic part. We have been unable to make compounds analogous to compound (3b) with two differently substituted aryl rings. For example, reaction of *p*-methoxybenzamidoxime with *N*-chlorosuccinimide in benzonitrile as solvent gave only the dimethoxy-analogue of base (3a)hydrochloride.

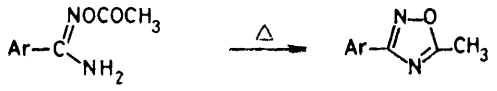




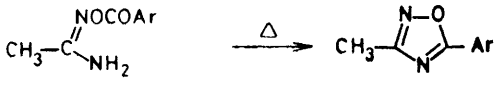
The negligible solvent effect (Table 3) would suggest a non-polar reaction, but the effect of change of solvent on this type of reaction would be better judged by examination of similar reactions. We have, accordingly, investigated the thermal cyclisation of amidoxime derivatives (14) and (16) to give 1,2,4-oxadiazoles (15) and (17).

This reaction, a common way to make 1,2,4-oxadi-

azoles, has been known since 1884,[14] and widely used,[15,16] but the mechanism has not been studied.[16] By choosing the series (14) and (16) we have been able to use the methyl signals in the ^{1}H n.m.r. spectra to follow the reactions, to use the mechanistic probes already employed



(14) (15)



(16) (17)

for the reaction of equation (i), and additionally to vary the substituent on the aryl rings to seek a possible Hammett correlation.

The kinetic results obtained for compounds (14) and (16) in diphenyl ether and in other solvents are given in Tables 4 and 5. First-order kinetics were obtained in every case, and we were able to include one hydroxylic solvent in these series. These cyclisations also proceeded with negative $\Delta S^{\ddagger}$ and showed only very small solvent effect. The sequence (16) ⟶ (17) was rather less susceptible to change of solvent than sequence (14) ⟶ (15), whilst being slightly faster under identical conditions in diphenyl ether (because of a slightly lower activation energy), but not in all solvents.

To avoid the dangers of adventitious water affecting the kinetic isotope effect studies, the rate of cyclisation of compound (14; Ar = Ph) was followed in diphenyl ether and in that solvent containing water (5 moles per mole of reactant), and the dideuterio-analogue of compound (14; Ar = Ph) (94% ND_2 by n.m.r.) was measured also in diphenyl ether with and without deuterium oxide (5 moles per mole) added. The results are given in Table 6. There was a kinetic isotope effect (k_H/k_D 1.5 in dry solvent, 1.4 in wet solvent), whilst the effect of added water was to increase the rate 1.4-fold, and of added deuterium oxide to increase the rate 1.5-fold for the unlabelled and labelled compounds respectively. The two cyclisations (14) ⟶ (15) and (16) ⟶ (17) were effected in deuteriochloroform by the addition of sodium hydride, at room temperature in <30 min.

TABLE 4

Kinetic results for reaction of compounds (14; Ar = Ph) and (16; Ar = Ph) in diphenyl ether [a]

(14; Ar = Ph)

Temp. (°C)	$10^5k/s^{-1}$	Average $t_{\frac{1}{2}}$/min
105.1	4.51, 4.22	265
115.2	9.87, 10.5	114
125.2	20.7, 20.7	56.8
135.1	46.4, 46.4	24.9
145.2	99.6, 92.4	12
100.0	2.8 (calc.)	412

E_a 24.4 ± 0.4 kcal mol^{-1}
$\Delta S^{\ddagger}$ −16.5 ± 1.1 cal K^{-1} mol^{-1} (at 125°)

(16; Ar = Ph)

Temp. (°C)	$10^5k/s^{-1}$	Average $t_{\frac{1}{2}}$/min
109.2	8.2, 7.5	147
120.0	19, 18	63
130.0	42, 40	28
140.3	84, 79	14
90.0	1.5 (calc.)	770
100.0	3.8 (calc.)	304
125.0	28 (calc.)	40.5

E_a 23.7 ± 0.4 kcal mol^{-1}
$\Delta S^{\ddagger}$ −17.8 ± 1.1 cal K^{-1} mol^{-1} (at 125°)

[a] Oil bath; see Experimental section.

TABLE 5

Rate constants for reaction of compounds (14; Ar = Ph) and (16; Ar = Ph)

Solvent	Temp. (°C)	Average k/s^{-1}	Relative k
(14; Ar = Ph) Diphenyl ether	125	2.0×10^{-4}	1.0
	100	2.8×10^{-5}	(1.0)
Nitrobenzene	125	1.7×10^{-4}	0.85
Ethylene carbonate	125	1.1×10^{-3}	5.5
[$^2H_6$]Dimethyl sulphoxide	125	1.2×10^{-3}	6.0
Benzyl alcohol	100	5.5×10^{-4}	(19.6)
(16; Ar = Ph) Diphenyl ether	125	2.8×10^{-4}	1.0
	120	1.8×10^{-4}	(1.0)
Nitrobenzene	120	1.1×10^{-4}	(0.6)
Ethylene carbonate	125	6.1×10^{-4}	2.2
[$^2H_6$]Dimethyl sulphoxide	125	3.4×10^{-4}	1.2
Benzyl alcohol	125	1.2×10^{-3}	4.3

[a] Variable temperature probe; see Experimental section.

TABLE 6

Rate constants for the reaction of deuteriated and undeuteriated acetyl derivatives at 125.2°

Compound	Solvent	$10^4k/s^{-1}$
$PhC(NH_2)=NOCOCH_3$	Ph_2O	2.2
$PhC(NH_2)=NOCOCH_3$	$Ph_2O + H_2O$	3.0
$PhC(ND_2)=NOCOCH_3$	Ph_2O	1.5
$PhC(ND_2)=NOCOCH_3$	$Ph_2O + D_2O$	2.2

Thus far, close parallels are seen between results for the cyclisation of equation (i) and these two cyclisations. To probe the electron-distribution in the transition states for these cyclisations, ring-substituted compounds (14) and (16) were cyclised, with the results shown in Table 7. For the cyclisations of *O*-acetylarylamidoximes (14) and *O*-aroylacetamidoximes (16) the detailed mechanism that accounts for all the evidence described above is shown in Scheme 4.

The equilibrium (14), (16) ⇌ (18) must lie well to the left, and the second step, proton-transfer, be rate determining, with the observed rate constant being [17] the product k_1k_2/k_{-1}. This mechanism allows a negative entropy of activation and a kinetic isotope effect for the loss of $-\overset{+}{N}H_2-$ proton (presumably to solvent). Any isotope effect on the initial equilibrium, which would be to make $(k_1/k_{-1})_H < (k_1k_{-1})_D$ by virtue of the more nucleophilic ND_2,[11] would be smaller than that on the second step. For a reaction involving polar intermediates, one would

normally expect to see a solvent effect, but since the equilibrium first stage involves creating a polar molecule (18), and the second involves generating a neutral molecule (19) from this, any solvent effect would be difficult to predict. Additionally, the solvent must play a role

TABLE 7

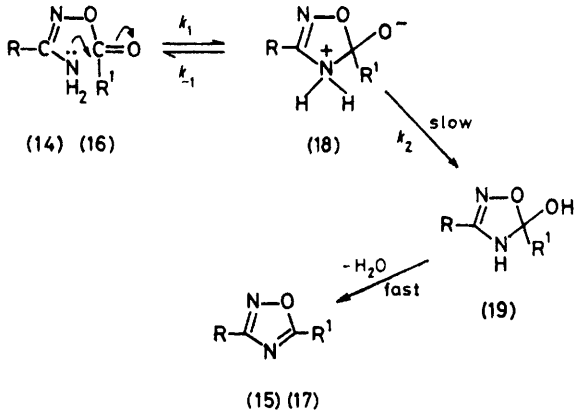
Rate constants for cyclisations (14) ⟶ (15) and (16) ⟶ (17) in diphenyl ether at 125.3°

Compound	$10^4k/s^{-1}$	Hammett correlation [a]
(14; Ar = C_6H_5)	2.1	
(14; Ar = p-$Me_2NC_6H_4$)	9.0	
(14; Ar = p-$MeOC_6H_4$)	3.4	ρ −0.79 (σ)
(14; Ar = p-BrC_6H_4)	1.35	
(14; Ar = m-ClC_6H_4)	1.2	
(14; Ar = p-$NO_2C_6H_4$)	0.46	
(16; Ar = C_6H_5)	2.8	
(16; Ar = p-$MeOC_6H_4$)	1.0	ρ +0.54 (σ^+)
(16; Ar = m-FC_6H_4)	4.6	
(16; Ar = p-$NO_2C_6H_4$)	6.95	

[a] Using σ values p-Me_2N, −0.83; p-MeO, −0.27; p-Br, 0.23; m-Cl, 0.37; p-NO_2, 0.78; m-F, 0.37; and σ^+ value p-MeO, −0.78.

in proton transfer, and solvent polarity (dielectric constant) and solvent basicity do not run parallel. It is to be noted that benzyl alcohol was the solvent with the largest effect on the reaction rate. The effect of sodium hydride on these cyclisations is to form an anion from the amidoxime derivative that far more readily ring-closes by nucleophilic addition to the carbonyl group than does the poorly nucleophilic neutral derivative itself.

That these cyclisations do indeed involve polar species was shown by the Hammett correlations. The observed reaction constants (ρ) will be the sum [18] of those for the equilibrium (14), (16) ⇌ (18) *via* the transition state (20), and the rate step (18) ⟶ (19). The effect of ring-substituent in (14) (ρ −0.79) is in accord with the amidoxime NH_2 group acting as nucleophile, with decrease of electron density at the amidoxime carbon,

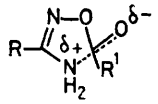


SCHEME 4

whilst the effect of ring substituent in (16) (ρ +0.54 correlating with σ^+) indicates loss of conjugation of the aryl ring with the carbonyl group.[19] Thus passage through the transition state (20) is the stage with most effect on the Hammett reaction constants.

The over-riding conclusion, that these cyclisations (14) ⟶ (15) and (16) ⟶ (17) involve a polar mechanism, and the very close correspondence of evidence gathered for them with that obtained for the reaction of equation (i) leads to the conclusion that this last reaction is also a polar one [*i.e.* equation (v)].

In the course of this study we have obtained ^{13}C n.m.r.



(20)

spectra for a range of substituted aryl oximes, amidoximes, and *O*-acetylamidoximes, 3-aryl-5-methyl-1,2,4-oxadiazoles, and 5-aryl-3-methyl-1,2,4-oxadiazoles. Using the substituent chemical shift values given by Abraham and Loftus,[20] together with normal off-resonance decoupling, we have assigned chemical shifts

TABLE 8

Substituent chemical shifts ($\Delta\delta_C$) in benzenes [a]

Substituent	C-1	*ortho*	*meta*	*para*
CH=NOH [b]	3.9	−1.5	−0.2	0.7
$C(NH_2)$=NOH	4.7	−2.7	−0.5	0.5
$C(NH_2)$=$NOCOCH_3$	2.7	−1.7	−0.2	1.7
C=NOC(CH_3)=N	−1.8	−1.2	0.1	2.3
C=NC(CH_3)=NO	−4.2	−0.3	0.6	3.2

[a] In p.p.m. from benzene (δ_C 128.5 p.p.m.), as in ref. 20. [b] Previous assignments (C. P. J. Vuik, M. ul Hasan, and C. E. Holloway, *J.C.S. Perkin II*, 1979, 1214) of *ortho*- and *meta*-carbons are incorrect.

to all the carbon atoms of these compounds, and have calculated average substituent chemical shift values to supplement those given in that text.[20] Table 8 and Supplementary Publication No. SUP 22887 (8 pp.).* give these results. Whilst these spectra have been obtained for deuteriochloroform solutions (occasionally

TABLE 9

^{13}C Chemical shifts (δ_C) for *para*-carbons in [$^2H_6$]-acetone for PhX

X	δ_{Cp}	$\Delta\delta_{Cp}$	σ_p^+
H	128.8	0	0
$C(NH_2)$=NOH	130.0	1.2	0.21
$C(NH_2)$=$NOCOCH_3$	131.2	2.4	0.33
C=NOC(CH_3)=N)	131.8	3.0	0.39
C=NC(CH_3)=NO	133.5	4.7	0.56

with a little [$^2H_6$]dimethyl sulphoxide added), the ^{13}C n.m.r. chemical shifts for the *para*-carbons of monosubstituted benzenes, in deuterioacetone solutions, allow calculation of σ^+ values, using the relationship [21] $\delta_C = 9.809\sigma^+ - 0.814$. Calculated σ^+ values for several substituents are given in Table 9.

* For details of Supplementary Publications, see Notice to Authors No. 7, in *J.C.S. Perkin II*, 1979, Index issue.

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls, and u.v. spectra for ethanolic solutions. N.m.r. spectra were recorded at 90 MHz for ^1H and 25.2 MHz for ^{13}C in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal reference.

O-Benzimidoylbenzamidoxime (3a).—*N*-Chlorosuccinimide (9.6 g) was added in portions to a stirred solution of benzamidoxime (10.0 g) in dried methylene chloride (80 ml). After 2 h, a solid was filtered off, washed several times with methylene chloride, and dried to give the hydrochloride salt (3a, HCl) (9.15 g, 91%), m.p. 131—132°, $\lambda_{max.}$ 238 and 275 nm, $\nu_{max.}$ *ca.* 3 180 and 1 630 cm^{-1}, τ(CDCl$_3$–[$^2H_6$]DMSO) 1.04br (s, 2 NH), 1.46 (d, *J* 8 Hz, 2 aryl H), and 2.0—2.6 (m, 8 aryl H), *m/e* 136 ($C_7H_8N_2O$, 100%), 119 (C_7H_5NO, 79), 104 (C_6H_5CNH, 57), 91 (C_6H_5N, 25), 77 (C_6H_5, 75), 64 (C_5H_4, 16), and 51 (C_4H_3, 35) (Found: C, 60.6; H, 4.8; N, 15.2. Calc. for $C_{14}H_{14}ClN_3O$: C, 61.0; H, 5.1; N, 15.2%). Attempts to crystallise the salt from hot ethanol gave 3,5-diphenyl-1,2,4-oxadiazole, m.p. 106—107° (lit.,[6] 106°).

This salt (3a, HCl) (9.15 g) was suspended in dried methylene chloride (100 ml) and triethylamine (5 ml) was added. The mixture was stirred at room temperature for 2 h, filtered, and the residue was washed several times with water, and dried to give *O*-benzimidoylbenzamidoxime (5.67 g, 71%), m.p. 123—124° (lit.,[3] 124—125°), $\lambda_{max.}$ 226 (ε 16 600) and 260(sh) nm (9 700), $\nu_{max.}$ 3 465, 3 270, 1 640, and 1 050 cm^{-1}, τ(CDCl$_3$–[$^2H_6$]DMSO) 1.50br (s, NH), 1.78 (m, 2 aryl H), 2.09 (m, 2 aryl H), *ca.* 2.48 (m, 6 aryl H), and 3.21br (s, NH_2), δ_C (CDCl$_3$–[$^2H_6$]DMSO) 162.0 (C=NH) and 156.0 p.p.m. (C=NO), *m/e* 240 (*M* + 1, 100%), 222 ($C_{14}H_{10}N_2O$, 69), 119 (C_7H_5NO, 100), 105 (C_6H_5CO, 81), 91 (C_6H_5N, 34), 89 (C_7H_5, 18), 77 (C_6H_5, 32), and 64 (C_5H_4, 25) (Found: C, 69.8; H, 5.4; N, 17.9. Calc. for $C_{14}H_{13}N_3O$: C, 70.3; H, 5.5; N, 17.6%).

O-(N-*Acetylbenzimidoyl*)*benzamidoxime* (3b).—*O*-Benzimidoylbenzamidoxime (2.0 g) was stirred in a mixture of chloroform (30 ml) and acetic anhydride (15 ml) at room temperature until solution took place (*ca.* 2 h). The volume was reduced, under vacuum, to 15 ml, and ice–water was added. The mixture was stirred until a precipitate formed which was filtered off, washed with water, dried, and crystallised from chloroform–light petroleum (b.p. 60—80°) to give the *acetyl derivative* (3b) (1.75 g, 74%), m.p. 135°, $\lambda_{max.}$ 238 (ε 19 000) and 265(sh) nm (10 000), $\nu_{max.}$ 3 480, 3 380, 1 695, and 1 645—1 630 cm^{-1}, τ 2.05 (m, 2 aryl H), 2.32 (m, 2 aryl H), 2.55 (m, 6 aryl H), 4.75br (s, NH_2), and 7.72 (s, CH_3), δ_C 182.5 (C=O), 156.0 (C=NO), 148.2 (C=NAc), and 27.5 p.p.m. (CH_3), *m/e* 282 (*M* + 1, 100%) and 281 (*M*, 79.5) (Found: C, 68.0; H, 5.3; N, 14.7. $C_{16}H_{15}N_3O_2$ requires C, 68.3; H, 5.4; N, 14.9%).

This product was crystallised from ethanol–water–deuterium oxide (2 : 1 : 1) to give a partially *N*-deuteriated product for i.r. study. The 95% *N*-deuteriated product was obtained by dissolving the derivative (3b) in acetone–deuterium oxide, evaporating off the acetone, and repeating this sequence.

O-(N-*Acetyl*-p-*methoxybenzimidoyl*)-p-*methoxybenzamidoxime*.—A sequence corresponding to that given above, starting with *p*-methoxybenzamidoxime gave the *hydrochloride* of the base, m.p. 198° (decomp.), $\lambda_{max.}$ 249 and 297 nm, and the *free base*, m.p. 114—115°, $\lambda_{max.}$ 261 nm, $\nu_{max.}$ 3 520, 3 330, and 1 650 cm^{-1}, τ 1.90 (d, *J* 9 Hz, 2 aryl H), 2.20 (d, *J* 9 Hz, 2 aryl H), 3.04 (d, 2 aryl H), 3.05 (d, 2 aryl H), 3.50br (s, NH_2), and 6.16 (s, 2 CH_3), δ_C 161.6, 161.5, 161.1 (C=NH, *para*-carbons), 155.2 (C=NO), 129.3, 128.2 (*ortho*-carbons), 124.5, 124.0 (C-1 and -1′ aryl carbons), 113.6, 113.3 (*meta*-carbons), and 55.1 p.p.m. (2 OCH_3) (Found: C, 64.0; H, 5.8; N, 14.4. $C_{16}H_{17}N_3O_3$ requires C, 64.2; H, 5.7; N, 14.0%), and finally O-(N-*acetyl*-p-*methoxybenzimidoyl*)-p-*methoxybenzamidoxime*, m.p. 125—128°, $\lambda_{max.}$ 262 and 275(sh) nm, $\nu_{max.}$ 3 520, 3 400, 1 695, and 1 640 cm^{-1}, τ 2.13 (d, *J* 9 Hz, 2 aryl H), 2.38 (d, *J* 9 Hz, 2 aryl H), 3.09 (d, 2 aryl H), 3.14 (d, aryl 2 H), 4.76br (s, NH_2), 6.16 (s, OCH_3), 6.26 (s, OCH_3), and 7.72 (s, CH_3), δ_C 182.6 (C=O), 162.8, 161.8 (*para*-carbons), 155.8 (C=NO), 148.3 (C=NAc), 130.2, 127.9 (*ortho*-carbons), 123.4, 123.2 (C-1 and -1′ aryl carbons), 114.2, 113.8 (*meta*-carbons), 55.4, 55.2 (2 OCH_3), and 27.6 p.p.m. (CH_3) (Found: C, 63.1; H, 5.4; N, 12.6. $C_{18}H_{19}N_3O_4$ requires C, 63.3; H, 5.6; N, 12.3%).

Reactions of O-(N-*Acetylbenzimidoyl*)*benzamidoxime*.—(a) *With acetyl chloride*. Acetyl chloride (2 ml) was added dropwise during 2 h to a stirred mixture of the acetyl compound (3b) (1.0 g), sodium carbonate (1.0 g), and magnesium sulphate (500 mg) in sodium-dried ether (80 ml) at room temperature. The solid was filtered off. The filtrate was washed with water (3 × 50 ml). The aqueous washings were saturated with sodium chloride and extracted with ether (2 × 50 ml). The combined ethereal solutions were dried and reduced in volume to *ca.* 1 ml, when *N*-acetylbenzamide (480 mg, 83%) was filtered off and shown to be identical with an authentic sample,[22] m.p. and mixed m.p. 115—116°.

The solid first filtered off was shaken with water (100 ml) and ether (75 ml). The organic layer was separated and the aqueous layer was saturated with sodium chloride and extracted with ether (2 × 50 ml). The combined ethereal extracts afforded *O*-acetylbenzamidoxime (580 mg, 92%) crystallised from chloroform–light petroleum (b.p. 60—80°) to have m.p. 94—94.5°, identical with that of an authentic sample.

(b) *With propionyl chloride*. A similar reaction using propionyl chloride in place of acetyl chloride gave *N*-acetylbenzamide (400 mg, 69%), and *O*-propionylbenzamidoxime (470 mg, 74%), m.p. 73.5—74.5°. Although Schulz [21] gives m.p. 93°, the spectroscopic and analytical data establish the structure: $\nu_{max.}$ 1 745 cm^{-1}, τ 2.29 (m, 2 aryl H), 2.55 (m, 3 aryl H), 4.49br (s, NH_2), 7.50 (q, CH_2), and 8.80 (t, CH_3) (Found: C, 62.7; H, 6.0; N, 14.8. Calc. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6%). Heating at 150° converted this product into 5-ethyl-3-phenyl-1,2,4-oxadiazole (an oil [23,24]), τ 1.95 (m, 2 aryl H), 2.55 (m, 3 aryl H), 7.08 (q, CH_2), and 8.62 (t, CH_3).

(c) *With toluene*-p-*sulphonyl chloride*. Toluene-*p*-sulphonyl chloride (250 mg) was added to the acetyl derivative (210 mg) in pyridine (15 ml) and was left at room temperature for 48 h. Normal work-up gave *N*-acetylbenzamide (50 mg, 42%) and benzamidoxime (40 mg, 40%).

(d) *With sodium hydride*. A suspension of sodium hydride (42 mg) in dry tetrahydrofuran (20 ml) was added to the acetyl derivative (38 mg) in the same solvent (20 ml). The mixture was stirred at room temperature for 1 h, filtered, and the filtrate was taken to dryness to leave a mixture (t.l.c. and n.m.r.) of 3,5-diphenyl-1,2,4-oxadiazole and acetamide.

Preparation of O-*Acetylarylamidoximes*.—The appropriate aromatic nitrile (*ca.* 3.5 g) was heated under reflux with hydroxylamine hydrochloride (1.8 g) and sodium hydroxide (1.0 g) in ethanol (40 ml) and water (20 ml) for 4 h. Most of the ethanol was distilled off when the amidoxime crystal-

lised on cooling, to be recrystallised from ethanol–water. Physical data and, where appropriate, analytical data are given in SUP 22887. The arylamidoxime (2.0 g) and acetic anhydride (5 ml) were left at room temperature for 18 h. The solution was poured into water–ice (250 g) and the resulting acetyl derivative was crystallised from ethanol–water. Physical data and, where appropriate, analytical data are given in SUP 22887.

Preparation of O-Aroylacetamidoximes.—Acetonitrile (35 ml), hydroxylamine hydrochloride (35 g), sodium hydroxide (20 g), ethanol (50 ml), and water (100 ml) were refluxed together for 60 h. The solvent was evaporated off and the crude mixture of acetamidoxime and sodium chloride (*ca.* 25 g) was stirred with 1M-sodium hydroxide (100 ml). The solution was filtered and the aroyl chloride (15 g) was added in portions with shaking. The precipitated *O*-aroylacetamidoxime was filtered off, dried, and crystallised from chloroform–ether. Physical data and, where appropriate, analytical data are given in SUP 22887.

Cyclisation of Amidoxime Derivatives.—These derivatives were heated neat at *ca.* 50° above their m.p.s for 2 h. Cooling and crystallisation from ethanol afforded the 3,5-disubstituted 1,2,4-oxadiazoles, listed in SUP 22887.

Kinetic Methods.—The sample (100—200 mg) and the solvent (5 ml) in a small stoppered flask were brought to temperature in a thermostatically controlled oil-bath (±0.1 °C). Samples (9 or 10) were pipetted out at intervals directly into n.m.r. tubes, and analysed from the sharp methyl signals of starting material and product acetamide or oxadiazole. It was found no more accurate to use internal standards. Duplicate reactions were followed for approximately two half lives. Rate constants were obtained graphically and were used to calculate the Arrhenius activation energies and entropies of activation for unimolecular reactions in solution [25] using a computer program that also gave estimated standard deviations. Comparative rates in different solvents were measured using the variable temperature probe of the Perkin-Elmer R 32 n.m.r. spectrometer.

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