Mononuclear Heterocyclic Rearrangements. Part 9.[1] A Kinetic Study of the Rearrangement of the *Z*-Phenylhydrazone of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole into 4-Benzoylamino-2,5-diphenyl-1,2,3-triazole in Methanol, Dioxan, Ethyl Acetate, and Acetonitrile

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The kinetics of the title reactions have been measured at various piperidine concentrations. The results obtained show that in all the solvents studied the rearrangements occur through a bimolecular reaction pathway involving one molecule of piperidine (k_{II}). However, depending on the solvent used more catalysed steps contribute to the overall reaction. Thus, in methanol, catalysis (k_{MeO}) by methoxide ion, derived from the basic ionization of piperidine in methanol, has also been observed and in dioxan or in ethyl acetate, besides the uncatalysed (k_u) and k_{II} steps, the overall mechanism involves a small contribution from catalysis by two molecules of piperidine (k_{III}). The results obtained in this work together with those previously obtained in benzene allow exclusion of the addition of piperidine to the C(5)–N(4) bond of the 1,2,4-oxadiazole ring. The k_{III} step is likely to arise from catalysis of catalysis.

Recently we reported data concerning the mononuclear heterocyclic rearrangement [2] (m.h.r.) of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (I-*Z*) into 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (II) in dioxan–water (DIOX–W),[3] in solutions buffered at various pS^+, and in benzene,[4] at various piperidine (PIP) concentrations.

We showed that in DIOX–W the rearrangement is general-base-catalysed and we determined the contribution of the single-reaction pathways (k_u, k_{OH}, and k_B) to the overall rate. On the other hand, the m.h.r. occurs in benzene *via* two base-catalysed routes requiring one and two molecules of piperidine, respectively. While the data obtained in DIOX–W and the second-order pathway in benzene agree with a transition state such as (III) the third-order term observed in benzene suggests a multistep mechanism where the second molecule of piperidine might, *e.g.* (a) exert catalysis of catalysis [4] (made necessary by the low polarity and the low basicity of benzene solvent) or (b) favour the progress of the reaction through an interaction with the 1,2,4-oxadiazole ring at the C(5)–N(4) bond, similar to Harsányi's [5] proposal for the rearrangement of other 1,2,4-oxadiazole derivatives.

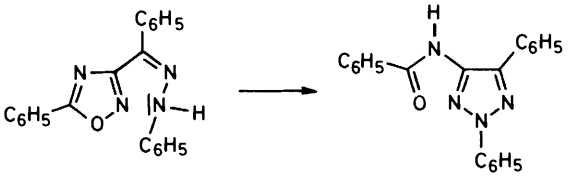
The kinetic data so far collected do not permit a choice between hypotheses (a) and (b). In fact, in DIOX–W there could also be a similar addition, to the C(5)–N(4) bond, of a molecule of water but clearly this is not detectable under the experimental conditions used. In order to gain information about the mechanism of catalysis we have followed some different paths.

(a) The piperidine-catalysed m.h.r. of (I-*Z*) has been studied in four more solvents, namely, methanol, ethyl acetate (EA), dioxan (DIOX), and acetonitrile (ACN), the first of which is similar to DIOX–W and the last three aprotic solvents differ from each other and from benzene in basicity and polarity.

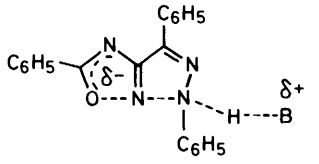
(b) The m.h.r. of the *Z*-*p*-nitrophenylhydrazone of 3-benzoyl-1,2,4-oxadiazole in benzene, promoted by a large number of primary, secondary, and tertiary amines and primary diamines with different electronic and steric requirements, has been examined.

(c) The m.h.r. of the *Z*-phenylhydrazone of some 5-substituted 3-benzoyl-1,2,4-oxadiazoles has been studied in different solvents.

The results for (a) and (b) form the subject of this and of the following paper, respectively.



(I-*Z*) (II)



(III)

Results

Rearrangement of (I-Z) *in Methanol.*—The apparent first-order kinetic constants k_A for the rearrangement of (I-*Z*) in methanol, at 313.15 K, as a function of (PIP), piperidine hydrochloride ($PIPH^+$), and methoxide ion concentrations † are summarized in Table 1. At constant methoxide ion concentration the k_A value increases linearly with increasing PIP concentration (items 1—9, 10—17, 18—25, and 26—33 in Table 1). Between the lowest and highest PIP concentration there is a several-fold increase in k_A leaving no doubt that the reaction is catalysed by piperidine. The results of a linear regression analysis of k_A values according to equation (1) show that k_{II}‡ does not depend on 'buffer

$$k_A = k_0 + k_{II}[PIP] \quad (1)$$

ratio' (Table 2). On the other hand the reaction is strongly accelerated by MeO^- (compare items 34 and 1; 36 and 10;

† Methoxide ion stems from the basic ionization of piperidine in methanol and the addition of $PIPH^+$ reduces its concentration according to the equilbrium $C_5H_{10}NH + MeOH \rightleftharpoons C_5H_{10}NH_2^+ + MeO^-$.

‡ k_{II} and k_{III} refer, respectively, to reaction pathways involving one molecule of substrate (I-*Z*) and one or two molecules of PIP.

Table 1. Apparent first-order rate constants for the rearrangement (I-*Z*) ⟶ (II) in methanol at 313.15 K

No.	$[PIP]_{st}$/M [a]	$[PIPH^+]_{st}$/M [a]	$10^5[MeO^-]$/M [b]	$10^4k_A/s^{-1}$ [c]
1	0.101	0.0200	3.68	1.41
2	0.232	0.0460	3.68	2.42
3	0.343	0.0680	3.68	3.21
4	0.473	0.0940	3.67	4.14
5	0.605	0.120	3.68	5.09
6	0.707	0.140	3.69	5.90
7	0.808	0.160	3.69	6.70
8	0.919	0.182	3.69	7.41
9	1.01	0.200	3.69	8.15
10	0.112	0.0166	4.91	1.70
11	0.208	0.0306	4.95	2.42
12	0.320	0.0471	4.95	3.25
13	0.408	0.0600	4.96	3.70
14	0.520	0.0765	4.96	4.75
15	0.766	0.113	4.95	6.53
16	0.908	0.134	4.94	7.50
17	1.02	0.150	4.96	8.42
18	0.114	0.0110	7.51	2.03
19	0.207	0.0200	7.52	2.78
20	0.341	0.0330	7.52	3.78
21	0.471	0.0456	7.53	4.64
22	0.589	0.0570	7.53	5.50
23	0.748	0.0725	7.52	6.74
24	0.908	0.0880	7.53	7.95
25	1.03	0.100	7.51	8.86
26	0.205	0.0100	14.7	3.64
27	0.339	0.0166	14.8	4.78
28	0.428	0.0210	14.8	5.41
29	0.520	0.0255	14.8	6.08
30	0.620	0.0304	14.8	6.83
31	0.780	0.0383	14.8	8.03
32	0.910	0.0446	14.8	9.03
33	1.02	0.0500	14.8	9.75
34	0.101	0.0500	1.47	1.12
35	0.114	0.100	0.832	1.12
36	0.112	0.030	2.72	1.37
37	0.208	0.100	1.52	1.94
38	0.208	0.050	3.03	2.16
39	0.320	0.100	2.34	2.88
40	0.520	0.050	7.58	5.05
41	0.612	0.200	2.23	5.06
42	0.628	0.100	4.58	5.46
43	0.520	0.030	12.6	5.81
44	0.612	0.050	8.92	5.82
45	0.769	0.100	5.61	6.62
46	0.628	0.030	15.2	7.11
47	0.769	0.050	11.2	7.42
48	1.04	0.200	3.80	8.52
49	0.780	0.030	18.9	8.55
50	1.04	0.100	7.59	8.86
51	0.910	0.030	22.0	9.91
52	1.03	0.030	24.9	11.2

[a] $[PIP]_{st}$ and $[PIPH^+]_{st}$ are stoicheiometric concentrations. [b] Values calculated using K_{PIP} 7.3 × 10^{-6} (J. R. Schaefgen, M. S. Newman, and F. H. Verhoek, *J. Am. Chem. Soc.*, 1944, **66**, 1847). [c] Rate constants are accurate to within ±3%. At $\lambda_{max.}$ 366 nm, log ε 4.22 ± 0.02.

35 and 18; 37, 38, and 11; 39 and 12; 14, 40, 43, and 29; 41 and 44; 42 and 46; 45 and 47; 31 and 49; 16 and 24; 32 and 51; 25 and 52; 48 and 50) as also indicated by the trend of k_0 values in Table 2.

Thus the rearrangement studied is general base-catalysed.[6] In order to obtain the catalytic constants of both PIP and MeO^- we have fitted the kinetic data of Table 1 (items 1—52) to equation (2) (see Table 4).

$$k_A = k_u + k_{II}[PIP] + k_{MeO}[MeO^-] \quad (2)$$

Table 2. Linear regression analysis [a] of apparent first-order kinetic constants, k_A, for the rearrangement (I-*Z*) ⟶ (II) in methanol, at 313.15 K according to equation (1)

Items	$10^5(k_0 \pm s_0)/s^{-1}$	$10^4(k_{II} \pm s_{II})/l\ mol^{-1}\ s^{-1}$	r
1—9	0.673 ± 0.029	7.38 ± 0.04	0.9999
10—17	0.854 ± 0.056	7.38 ± 0.09	0.9995
18—25	1.20 ± 0.03	7.41 ± 0.05	0.9998
26—33	2.19 ± 0.05	7.48 ± 0.07	0.9997

[a] s_0 and s_{II} are the standard deviations of the regression parameters k_0 and k_{II}, respectively; r is the correlation coefficient. The items are identified according to the numbers in Table 1. The confidence levels for significance of k_{II} are all better than 99.9%.

The excellent adherence of the kinetic data to equation (2) while supporting a multilinear form for the law for general base catalysis shows that there is no significant contribution to catalysis by third-order terms, as already observed in dioxan–water [3] and at variance with observations for benzene.[4]

The calculated values of k_u, k_{II}, and k_{MeO} follow the order expected for the relative catalytic efficiency of the catalysts involved: a Brönsted plot (not shown) gives β 0.25 (*n* 3, *r* 1.000).

The k_u value calculated is similar to that observed in dioxan–water (1.2 × 10^{-6} s^{-1})[7] indicating parallel behaviour for the reaction in the two hydroxylic solvents.

The values of k_{Iyate} (respectively k_{OH} and k_{MeO} in the two solvents) are of the same order of magnitude, the three-fold difference being related to the variation in the properties of solvent and in the strength of the catalysing base.

Rearrangement of (I-Z) *in DIOX and EA.*—The apparent first-order kinetic constants, k_A, for the rearrangement of (I-*Z*) in DIOX and EA, in the presence of piperidine are summarized in Table 3. The results obtained point to a strong dependence of k_A on piperidine concentration. In both solvents a plot of k_A *versus* [PIP] shows a more than linear increase of k_A with increasing [PIP]. As a consequence in the range of concentrations where the contribution of the uncatalysed pathway to the overall rate can be neglected the corresponding plots of k_A/[PIP] *versus* [PIP] are linear. The second- and third-order catalytic constants calculated are shown in Table 4.

The low ratio between k_{III} and k_{II} (*ca.* 3 in both solvents) indicates * (a) that in addition to the uncatalysed step, measured by k_u, there is only one genuinely catalysed reaction pathway, *i.e.*, that involving *only one* molecule of piperidine, and/or (b) that the third-order reaction route makes only a minor contribution to the overall rate.

Rearrangement of (I-*Z*) *in ACN.*—The apparent first-order kinetic constants, k_A, for the rearrangement of (I-*Z*) in ACN in the presence of piperidine are shown in Table 3. Also in this case the reaction rate depends on piperidine concentration but here the plot of k_A *versus* [PIP] is linear and the kinetic data can be treated according to the least-squares method giving first- and second-order constants as intercept and slope of the straight line, respectively.

Thus the mechanism of m.h.r. in ACN involves an uncatalysed reaction pathway and again a route involving *only one* molecule of piperidine.

* In many other cases [8] a low ratio between the apparent third- and second-order catalytic constants has been related to a medium effect arising from the addition of increasing amounts of a polar substance (*e.g.* piperidine) to a solvent of poor polarity.

Table 3. Apparent first-order rate constants [a] for the rearrangement (I-*Z*) ⟶ (II), k_A, in various solvents at 313.15 K, in the presence of piperidine

Benzene [b]													
[PIP]/M	0.0255	0.0510	0.102	0.210	0.350	0.410	0.610	0.710	0.770	0.850	0.950	1.01	
$10^5k_A/s^{-1}$	0.0136	0.0370	0.114	0.40	1.06	1.42	3.04	4.11	4.81	5.76	7.29	8.08	
Dioxan [c]													
[PIP]/M	0.0048	0.0096	0.0225	0.0480	0.0950	0.160	0.280	0.398	0.600	0.720	0.790	0.895	0.995
$10^5k_A/s^{-1}$	0.0350	0.0520	0.0877	0.180	0.385	0.737	1.63	2.82	5.39	7.27	8.43	10.5	12.7
Ethyl acetate [d]													
[PIP]/M	0.0049	0.0098	0.0245	0.0490	0.0950	0.166	0.248	0.360	0.497	0.618	0.760	0.910	1.04
$10^5k_A/s^{-1}$	0.0569	0.0847	0.174	0.340	0.702	1.44	2.61	4.36	7.24	10.5	15.1	20.5	25.8
Acetonitrile [e]													
10^2[PIP]/M	0.147	0.315	0.580	1.10	1.42	2.02	2.51	3.03	3.51				
$10^3k_A/s^{-1}$	0.620	1.88	3.06	5.29	6.77	9.45	11.7	14.0	16.2				

[a] Rate constants are accurate to within ±3%. [b] [(I-*Z*)] 1.47 × 10^{-4}M. Kinetic data at [PIP] > 0.2M from ref. 4. [c] [(I-*Z*)] 1.66 × 10^{-4}M. At $\lambda_{max.}$ 366 nm, log ε 4.22 ± 0.02. [d] [(I-*Z*)] 1.70 × 10^{-4}M. At $\lambda_{max.}$ 366 nm, log ε 4.22 ± 0.02. [e] [(I-*Z*)] 1.74 × 10^{-4}M. At $\lambda_{max.}$ 364 nm, log ε 4.23 ± 0.02.

Table 4. Linear regression analysis [a] of apparent first-order kinetic constants for the rearrangement (I-*Z*) ⟶ (II), at 313.15 K, according to equations (2) and (4)

Solvent	$k_u \pm s_u$/ s^{-1}	$k_{II} \pm s_{II}$/ l mol^{-1} s^{-1}	$k_{III} \pm s_{III}$/ l^2 mol^{-2} s^{-1}	*n*	*R*	k_{III}/k_{II}/ l mol^{-1}	ε	*E*	*B*
Benzene	0 [b]	(3.21 ± 0.04)10^{-6}	(7.65 ± 0.06)10^{-5}	9	0.9999	24	2.3	1.93	48
Dioxan	2 × 10^{-7} [b]	(3.18 ± 0.05)10^{-5}	(9.60 ± 0.08)10^{-5}	10	0.9997	3.0	2.2	3.98	237
Ethyl acetate	3 × 10^{-7} [b]	(5.74 ± 0.11)10^{-5}	(1.83 ± 0.02)10^{-4}	10	0.9995	3.2	6.0	(0)	181
Acetonitrile [c]	(2.78 ± 0.88)10^{-4}	(4.54 ± 0.04)10^{-1}		9	0.9997		37.5	5.21	160
Methanol [d]	(1.67 ± 0.18)10^{-5}	(7.40 ± 0.03)10^{-4}		52	0.9998 [e]		32.7	14.9	218

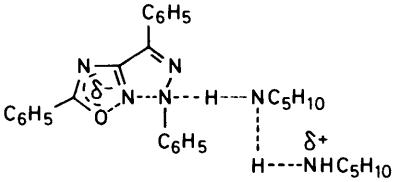
[a] s_u, s_{II}, and s_{III} are the standard deviations of the regression parameters k_u, k_{II}, and k_{III}, respectively. *R* is the correlation coefficient. The confidence levels for significance of regression parameters are all better than 99.9%. [b] See Experimental section. [c] Kinetic data have been analysed according to the equation: $k_A = k_u + k_{II}$[PIP]. [d] $k_{MeO} = 1.39 \pm 0.02$ l mol^{-1} s^{-1} [see text, equation (2)]. [e] Multiple correlation coefficient.

Discussion

The catalytic coefficients pertaining to the single steps of m.h.r. in various solvents are collected in Table 4 * where there are also some parameters related to the properties (ε, *E*, *B*) of the solvents used.[9]

The catalytic pattern of m.h.r. in MeOH is, as expected, similar to that observed in DIOX–W and supports the general-base-catalysed mechanism proposed for the rearrangement.[3] As to whether, in these two protic solvents or in C_6H_6, the addition of a base molecule to the C(5)–N(4) bond of 1,2,4-oxadiazole represented a real mechanistic alternative, the data now obtained in DIOX, EA, and ACN seem to give a clearcut answer. In fact the sharp decrease in the k_{III}/k_{II} ratio on going from C_6H_6 to EA and DIOX (k_{III}/k_{II} 24, 3, and 3.2, respectively) and the absence of a third-order apparent catalytic constant in ACN (a polar and basic aprotic solvent) are not consistent with the above hypothesis of an interaction of the second base molecule with the 1,2,4-oxadiazole ring. On the other hand the observation of a third-order reaction pathway in C_6H_6 strongly suggests a catalysis of catalysis (made necessary by the low polarity and the low basicity of the solvent) *i.e.* a reaction pathway in which the second molecule helps the first molecule of piperidine to disperse its incipient positive charge [as indicated in (IV)].

The relative magnitude of the catalytic kinetic constants deserves some comments. Among those studied by us, C_6H_6 is clearly the worst solvent for the m.h.r.; in fact it is characterized by a low dielectric constant, as well as by low electrophilic and nucleophilic constants.[9] In consequence we measured low absolute kinetic constants and a high k_{III}/k_{II} ratio in this solvent. Going to EA and DIOX the situation changes; these two solvents are strongly nucleophilic and therefore they help base catalysis by piperidine. In consequence we have observed higher k_u and k_{II} values and lower k_{III}/k_{II} ratios than in C_6H_6 [for the significance of $(k_{III}/k_{II})_{PIP}$ in DIOX and in EA see above].



(IV)

In MeOH and ACN we have not found the third-order reaction pathway and, as expected on the basis of the properties of these solvents, we have observed the highest k_u values. The relatively low k_{II} values observed in MeOH are likely to depend on the electrophilic character of this solvent, which strongly solvates the piperidine molecule giving rise to an unfavourable desolvation energy factor. The k_u and k_{II} values measured in ACN and the high reactivity of (I-*Z*) in dimethyl sulphoxide (DMSO) and in dimethylformamide (DMF) indicate that the aprotic dipolar solvents are the best solvents for the m.h.r.[10]

This kinetic behaviour agrees with the observation that 3-phenylthioureido-5-methylisoxazole rearranges at room temperature to 3-acetonyl-5-phenylamino-1,2,4-thiadiazole very slowly in chloroform and in C_6H_6, faster in ethanol, and

* In order to calculate the catalytic constants for the m.h.r. in C_6H_6 we have used, in addition to our previous data,[4] experimental results obtained in the range of low piperidine concentrations ([PIP] < 0.2M).

somewhat more rapidly in DMSO.[11] Moreover some 1,2,5-oxadiazole derivatives, which do not react in protic or dipolar solvents, undergo m.h.r. only under forcing conditions, *i.e.* by heating with bases in DMSO or in DMF.[12]

Experimental

Synthesis and Purification of Compounds.—Compounds (I-*Z*) and (II),[7] piperidine,[13] methanol,[13] dioxan,[13] ethyl acetate,[14] and acetonitrile [14] were prepared and/or purified according to the methods reported.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described [3] by measuring the disappearance of (I-*Z*) at the wavelength of its absorption maximum (data in Tables 1 and 3), where (II) practically does not absorb.

Calculations.—The more than linear increase of k_A with increasing [PIP] in C_6H_6, DIOX, or EA agrees with the general catalysis law described by equation (3). In the range of

$$k_A = k_u + k_{II}[PIP] + k_{III}[PIP]^2 \quad (3)$$

piperidine concentrations where the uncatalysed pathway, as measured by k_u, represents only a very small contribution to the overall rate, equation (3) can be rearranged into (4) and

$$k_A/[PIP] = k_{II} + k_{III}[PIP] \quad (4)$$

this allows the second- (k_{II}) and third-order (k_{III}) catalytic constants to be calculated by the least-squares treatment (see Table 4).

While for C_6H_6 a plot (not shown) of k_A/[PIP] *versus* [PIP] is linear over the whole range studied (0.0255—1.01M), in the case of DIOX and EA at piperidine concentrations as low as 0.025M the k_A values measured are greatly different from those calculated ($k_{calc.}$) by equation (4). Apparently the term k_u is not zero for these two solvents. Indeed, an estimate of this constant can be obtained by the differences $k_A - k_{calc.}$ for the points at [PIP] $\leq$ 0.025M. The average values of k_u so obtained are shown in Table 4.

Alternatively, we have used the multiple linear regression analysis of k_A values according to equation (3), but the least-squares method, which underestimates the points at low piperidine concentrations, gives intercepts (k_u) statistically not different from zero for DIOX and EA also. On the other hand we have measured [15] the apparent first-order kinetic constants for the rearrangement in C_6H_6, DIOX, and EA, in the absence of piperidine and the agreement between k_u estimated as above and the 'experimental' value is really good.

Acknowledgements

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