# Mononuclear Heterocyclic Rearrangements. Effect of the Structure of the Side Chain on the Reactivity. Part 1. Rearrangement of Some 3-Arylureines of 5-Phenyl-1,2,4-oxadiazole into 1-Aryl-3-benzoylamino-1,2,4-triazolin-5-ones in Acetonitrile, Benzene, and Dioxane–Water

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The effect of the structure of the side chain both on the mechanism and the reactivity in mononuclear heterocyclic rearrangements has been studied by comparing the base-catalysed rearrangement of some 3-arylureines of 5-phenyl-1,2,4-oxadiazole with that of some arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole. In acetonitrile and in benzene, in the presence of amines, on changing from the side chain CNN (arylhydrazones) to the side chain NCN (arylureines), a strong decrease of the reactivity has been observed (rate ratios *ca.* $10^3$), but the reaction mechanism is the same for the two series of compounds. In contrast, in dioxane–water, the reactivity variation is much less (rate ratios *ca.* 25 in the $pS^+$-dependent range) and a change of mechanism is observed. For arylureines and for arylhydrazones, specific- and general-base catalysis respectively has been shown. This is in keeping with the high acidity of arylureines, which in the presence of a strong base can be converted into the corresponding anions and then rearrange to the 1,2,4-triazolin-5-ones.

The rearrangement of heterocycles containing suitable side-chains represents an interesting method for the synthesis of heterocyclic derivatives. For example, through the mononuclear heterocyclic rearrangements (mhr),[1] some 1,2,4-oxadiazole, isoxazole, or 1,2,5-oxadiazole derivatives, bearing at C-3 a side-chain with one of the groups CNO, NCO, CCO, CNN, NCN, NCS, NNN, NCC, or CCN, can be more or less easily rearranged into 1,2,5- and 1,2,4-oxadiazole, isoxazole, 1,2,3- and 1,2,4-triazole, 1,2,4-thiadiazole, tetrazole, imidazole, and pyrazole derivatives (see Scheme 1). A great deal of qualitative


(1) (2)

A,B; C– or N
XYZ; CNO, NCO, CCO, CNN, NCN, NCS, NNN, NCC, CCN

**Scheme 1.**

data has been collected,[1a] and these indicate that the rearrangement rates depend on various factors, including the structure of the starting heterocycle and of the side chain and the reaction conditions (the reactions can be carried out by heating the solid compound or the compound in solution). The reaction temperature, the nature of the solvent used, and the addition of bases or acids can also largely affect the reactivity.

Previously in our investigations on mhr we have addressed our attention to the study of the rearrangement of the *Z*-arylhydrazones of some 3-benzoyl-isoxazoles[2] and -1,2,4-oxadiazoles[3] (final ring: 1,2,3-triazole), thereby gaining useful information on the reaction mechanism. In these mhr many parameters were changed, including the reaction conditions, the starting ring, and the substituent present in the arylhydrazone moiety, but the side chain at C-3 (CNN) was the same throughout. In order to gain information on the effect of the structure of the side chain on the reactivity in mhr we have performed various studies (including kinetic studies of heterocyclic compounds containing some new side chains, the latter being those for which qualitative studies have indicated either a lower (NCN: arylureino side chain), or a larger (NCN: arylformamidino side chain; NCS: arylthioureino side chain) reactivity with respect to the CNN side chain.[1a,4]

In this paper we present a complete study {including the effects of the solvent [acetonitrile (ACN), benzene (PhH), and dioxane–water (DIOX–W)], the base [piperidine (PIP), butylamine (BuA), triethylamine (TEA), diazabicyclo[2.2.2]-octane (DABCO), and borate buffers)], and the substituent (*p*-OMe, H, *p*-Cl, *m*-Cl, *m*-$NO_2$, or *p*-$NO_2$) present in the aryl group} on the reactivity of the mhr of some 3-arylureines of 5-phenyl-1,2,4-oxadiazole (**3a–f**).

It is known that (**3b**) stays unchanged by melting, but it rearranges (see Scheme 2) into 3-benzoylamino-1-phenyl-1,2,4-triazolin-5-one (**4b**) in high yield on being refluxed with aqueous KOH in ethanol, without any competing formation of 5-anilino-3-benzoylamino-1,2,4-oxadiazole (**5b**).[4c] Therefore the arylureino side chain, which can be considered as either a NCN or a NCO sequence, actually behaves only as a NCN sequence. In contrast, 5-phenyl-3-ureino-1,2,4-oxadiazole (**6**) does not rearrange by melting or refluxing with NaOH in ethanol and only the formation of hydrolysis products has been observed.[4b,*]

## Results and Discussion

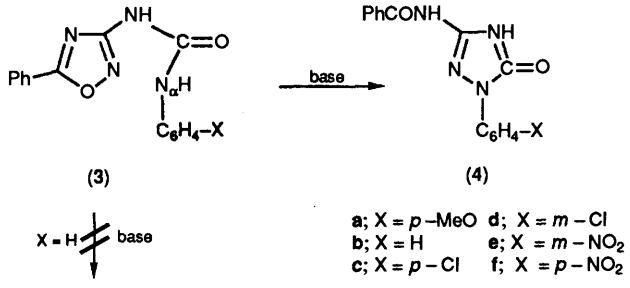
*Rearrangement of Some* 3-*Arylureines of* 5-*Phenyl*-1,2,4-*oxadiazole* (**3a–f**) *in ACN in the Presence of Piperidine:*

* In a subsequent paper we shall study the reactivity of some 3-arylformamidino- and/or 3-arylthioureino-isoxazoles (see above) and -1,2,5-oxadiazoles with the aim of obtaining kinetic data on the rearrangement of some 1,2,5-oxadiazole (a ring which shows a very low tendency to give mhr reactions)[1a] derivatives, and to gain information on the effect both of the side chain and of the starting heterocycle structure.

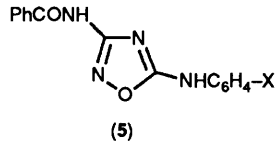
**Table 1.** Linear regression analysis[a] of apparent first-order kinetic constants for the rearrangements (**3a–f**)→(**4a–f**) in acetonitrile at 313.15 K in the presence of piperidine, according to equation $k_A = k_{II}[PIP] + i$.

| Compd. | $10^5(i \pm s_i)$ | $10^4(k_{II} \pm s_{II})$/ dm$^3$ mol$^{-1}$ s$^{-1}$ | $r$ | $n$ | $-\log k_{II}$ | $\sigma^n$ |
|---|---|---|---|---|---|---|
| (**3a**) | 0.063 ± 0.030 | 1.41 ± 0.00 | 0.9999 | 9 | 3.851 | −0.09 |
| (**3b**) | 0.079 ± 0.040 | 2.04 ± 0.01 | 0.9999 | 8 | 3.690 | 0.000 |
| (**3c**) | −0.014 ± 0.005 | 9.46 ± 0.08 | 0.9998 | 8 | 3.024 | 0.29 |
| (**3d**) | 0.015 ± 0.011 | 19.6 ± 0.2 | 0.9997 | 9 | 2.708 | 0.373 |
| (**3e**) | 0.046 ± 0.002 | 120 ± 0 | 0.9999 | 8 | 1.921 | 0.710 |
| (**3f**) | 0.019 ± 0.007 | 453 ± 3 | 0.9999 | 9 | 1.344 | 0.945 |

[a] $s_i$ And $s_{II}$ are the standard deviations of the regression parameters $i$ and $k_{II}$, respectively; $r$ is the correlation coefficient; $n$ is the number of points. The confidence levels for significance of regression parameters are all >99.9%.

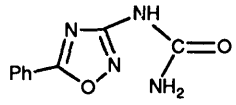



(3) (4)




(5)

**Scheme 2.**




(6)

*Reactivity and Substituent Effects.*—The reactivity of compounds (**3a–f**) has been studied in the presence of piperidine at 313.15 K. The apparent pseudo-first-order kinetic constants measured (Table A of a supplementary publication)* are dependent on piperidine concentration and fit well equation (1).† The results of the statistical analysis of data are reported in

$$k_A = k_{II}[B] \quad (1)$$

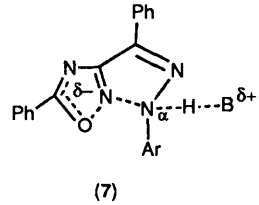
Table 1. The very low values of the intercept, the high uncertainty observed in some cases (**3a**, **b**, and **d**) and the negative value observed in one case (**3c**) suggest that the uncatalysed pathway ($k_u$) does not give any significant contribution to the reaction pathway. This kinetic behaviour agrees with the observation that (**3b**) does not rearrange when melted.[4c]

The present substituents largely affect the reactivity: on going from *p*-MeO to *p*-$NO_2$ substituent a large increase [$(k_{II})_{p\text{-}NO_2}/(k_{II})_{p\text{-}MeO}$ *ca.* 320] of the reactivity has been observed, but a reactivity logarithmic plot *versus* $\sigma^n$, $\sigma^H$, and/or $\sigma_p^-$ shows a deviation for (**3f**). In fact, for compounds (**3a–e**) an excellent free energy linear plot *versus* $\sigma^n$ can be obtained (ρ 2.45 ± 0.08, *i* 0.02 ± 0.03, *r* 0.998, *n* 5, CL >99.9%) and the point for X = *p*-$NO_2$ (**3f**) appears to require a substituent constant between $\sigma^n$ and $\sigma_p^-$, as in the reactivity variations of the *Z*-arylhydrazones (the substituent in the arylhydrazonic moiety ranging from hydrogen to the nitro group) of 3-benzoyl-5-phenyl-1,2,4-oxadiazole either in DIOX in the presence of piperidine or in DIOX–W in the presence of buffers. In those cases we calculated $r^-$ terms, in the Yukawa–Tsuno treatment, as 0.37 and 0.57–0.60, respectively.[3l,g]

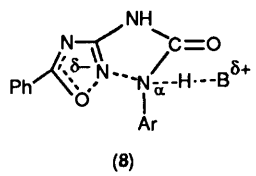
In the present case the calculation of the $r^-$ term has no meaning because we have studied only one electron-withdrawing substituent able to give through-resonance, but $r^-$ appears to be much the same as those previously obtained.[3l] In fact, we have added the point for X = *p*-$NO_2$ to the previous free energy relationship using $r^-$ 0.37 and observed again an excellent plot with the same susceptibility constant (ρ 2.45 ± 0.05, *i* 0.02 ± 0.03, *r* 0.999, *n* 6, CL >99.9%).

A comparison between the two side chains studied (CNN and NCN, respectively) in *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole and 5-arylureines (**3a–f**), shows that *Z*-arylhydrazones rearrange faster than arylureines and that the ratios of the rate constants appear to be substituent dependent; at 313.15 K the calculated ratios for X = *p*-MeO, H, and *p*-$NO_2$ are 3 000, 2 200, and 1 300 (estimated value), respectively, *i.e.*. the reactivity ratios decrease as the acidity of the hydrogen atom of arylureines increases.

Moreover the free energy plot for the reaction of the *Z*-arylhydrazones in DIOX in the presence of piperidine is a non-linear upward-concave plot and can be divided into two parts, the first containing substituents with a negative substituent constant (*p*-MeO and *p*-Me), and the second containing substituents with a substituent constant near to zero or largely positive (from *m*-$CH_3$ to *p*-$NO_2$). This therefore indicates a changeover of mechanism with changing substituent.[5] Indeed in the transition state (**7**) of these mhr the present substituent, affects both the acidity of the arylhydrazone hydrogen ($N_\alpha$–*H*) and the nucleophilicity of the $N_\alpha$ atom. Therefore it can cause a change in the structure of the transition state; so determining a different timing of nitrogen–nitrogen [$N_\alpha$–N(2)] bond formation (which causes an increase in the reactivity of *Z*-arylhydrazones containing strong electron-donating substituents), or of nitrogen–hydrogen ($N_\alpha$–*H*) bond breaking (which causes an increase in the reactivity of arylhydrazones containing substituents with a low electron-donating or with an electron-withdrawing effect).




(7)




(8)

In contrast, the free energy plot for the reaction of 3-arylureines (**3a–f**) is linear, indicating a unique structure for the transition state (**8**), in accordance with the expectation that the nitrogen atom of arylureine is much less nucleophilic than the nitrogen atom ($N_\alpha$) of arylhydrazones, and that the hydrogen atom of arylureines is more acidic than that of *Z*-arylhydrazones. Therefore, whatever the substituent, the reactivity depends on the degree of the nitrogen–hydrogen bond rupture (as also

* See the Experimental section.

† $k_u$, $k_{II}$, $k_{III}$, and $k_{IV}$ refer to reaction pathways involving one molecule of arylureine (**3**) and no (uncatalysed pathway), one, two, or three molecules (catalysed pathways) of amine, respectively.

**Table 2.** Linear regression analysis[a] of apparent first-order kinetic constants for the rearrangement (**3f**)→(**4f**) in acetonitrile at 313.15 K in the presence of various amines, according to equation $k_A = k_{II}[B] + i$.

| B | $10^4(i \pm s_i)$ | $10^3(k_{II} \pm s_{II})$/ l mol$^{-1}$ s$^{-1}$ | $r$ | $n$ |
|---|---|---|---|---|
| Piperidine | 0.002 ± 0.001 | 45.3 ± 0.3 | 0.9999 | 9 |
| n-Butylamine | 0.04 ± 0.02 | 6.07 ± 0.02 | 0.9999 | 8 |
| Triethylamine | 0.05 ± 0.07 | 6.78 ± 0.04 | 0.9999 | 8 |
| DABCO | 0.06 ± 0.06 | 4.63 ± 0.03 | 0.9999 | 8 |

[a] As for Table 1.

**Table 3.** Values of $k_2$ and $K_1$ calculated from equations (14) and (15).

| Compd. | $10^4k_2$/s$^{-1}$ | $K_1$/l mol$^{-1}$ |
|---|---|---|
| (**3a**) | 5.50 | 1 670 |
| (**3b**) | 6.40 | 1 970 |
| (**3c**) | 9.61 | 3 900 |
| (**3d**) | 10.7 | 4 750 |
| (**3e**) | 17.2 | 9 130 |
| (**3f**) | 31.0 | 32 650 |

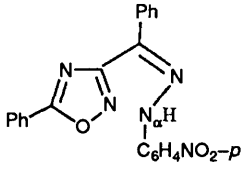
indicated by the requirement in the lfer for the *p*-nitro substituent of a substituent constant value intermediate between those of $\sigma^H$ and $\sigma_p^-$), and the course of the reaction can be depicted as in equations (2) and (3) (SH represents the substrate containing an acidic hydrogen atom).

$$SH + B \rightleftharpoons [S \cdots H \cdots B]^{\ddagger} \quad (2)$$

$$[S \cdots H \cdots B]^{\ddagger} \longrightarrow \text{products} \quad (3)$$

*Amine-catalysed Rearrangement of* 3-(p-*Nitrophenyl*)*ureine of* 5-*Phenyl*-1,2,4-*oxadiazole* (**3f**) *in ACN: Effect of the Amine Structure.*—The effect of the amine structure has been studied at 313.15 K using a primary (BuA) and two tertiary amines (TEA and DABCO), in addition to a secondary amine (PIP, see above). The apparent pseudo-first-order kinetic constants measured (see Table A of a supplementary publication) increase with increasing amine concentration and fit well equation (1). The results of the statistical analysis reported in Table 2 show that the uncatalysed pathway ($k_u$) does not give any significant contribution to the reaction (see above).

These results parallel those observed for the (*Z*)-p-nitrophenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**9**) at




(**9**)

283.15 K in ACN in the presence of the same amines,[2b] so indicating that similar mechanisms for the rearrangement of (**3f**) and (**9**) are operating and therefore in both substrates the reactivity is dependent on the degree of the nitrogen–hydrogen ($N_\alpha$–*H*) bond breaking. Accordingly, a plot of log ($k_{II}$) (**3f**) at 313.15 K *versus* log $(k_{II})_{(9)}$ at 283.15 K is linear (*s* 1.01 ± 0.06, *r* 0.997, *n* 4, C.L. >99.9), and the intercept (*i* 1.96 ± 0.12) represents the logarithmic average ratio between the reactivity in ACN of (**9**) at 283.15 K and of (**3f**) at 313.15 K. This confirms, for similar aryl substituents, the larger reactivity of the (*Z*)-arylhydrazone (**9**) with respect to the arylureine (**3f**), for all the amines tested. In fact, although the reactivity of (**9**) has been measured at a temperature 30° lower than that used for (**3f**), (**9**) is *ca.* 100 times more reactive than (**3f**).

*Amine-catalysed Rearrangement of* (**3f**) *in* PhH: *Effect of the Amine Structure.*—The effect of the amine structure has been studied at 313.15 K using a primary amine (BuA), a secondary cyclic amine (PIP), and two tertiary amines (TEA and DABCO). (The apparent pseudo-first-order kinetic constants measured are collected in Table B of a supplementary publication.) The reactivity of (**3f**) with the tertiary amines studied appears too low to give significant results (*e.g.* at [TEA] 1 mol dm$^{-3}$ and at 313.15 K $k_A < 10^{-9}$ s$^{-1}$; the extrapolated value in ACN at the same amine concentration is $k_A$ *ca.* $7 \times 10^{-3}$ s$^{-1}$). In contrast, (**3f**) reacts with BuA and PIP, giving $k_A$ values dependent on amine concentration, which fit well equations (4) and (5), respectively, as indicated by the results of

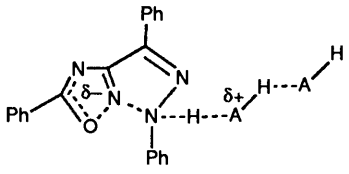
$$k_A = k_{IV}[B]^3 \quad (4)$$

$$k_A = k_{II}[B] + k_{III}[B]^2 \quad (5)$$

the statistical analysis [B = BuA: $k_{IV}$ (1.83 ± 0.02) × 10$^{-6}$, *i* 0.00 ± 0.01, *n* 9, *r* 0.998; B = PIP: $k_{II}$ (0.805 ± 0.016) × 10$^{-6}$, $k_{III}$ (3.51 ± 0.03) × 10$^{-6}$, *n* 8, *r* 0.9998]. The kinetic data again show a lower reactivity of (**3f**) as compared with (**9**) [at 313.15 K, for B = BuA: $(k_{IV})_{(9)}/(k_{IV})_{(3f)}$ *ca.* 830 and for B = PIP: $(k_{III})_{(9)}/(k_{III})_{(3f)}$ *ca.* 810, respectively].

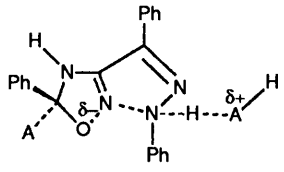
The behaviour of (**3f**) with BuA is similar to that of (**9**); on the other hand, (**3f**) rearranges in the presence of PIP through two different reaction pathways, one requiring one molecule and the other requiring two molecules of bases, respectively, while (**9**) reacts only through the pathway requiring two molecules of PIP.[3e] The higher acidity of the hydrogen atom ($N_\alpha$–*H*) of (**3f**) with respect to that of (**9**) well accounts for this behaviour, in fact (**3f**) can follow a reaction pathway which does not require a 'catalysis of catalysis'[3d,e,i–k,6] (see below). Moreover, it must be pointed out that amines affect the course of the reaction in different ways, depending on the nature of the solvent. In ACN (a basic, dipolar, and aprotic solvent, which strongly favours the rearrangement) the reaction requires only one molecule of amine, in PhH (an apolar solvent) the reaction needs one, or two, or three molecules of amine.

These results indicate, as already observed in the rearrangement of the *Z*-arylhydrazones of 3-benzoyl-1,2,4-oxadiazole and of 3-benzoylisoxazole, that the course of mhr depends on the structure of the amine used (primary, secondary, or tertiary)[3i,2b] and, for the same amine, on the nature of the solvent (polar or apolar).[3i,2b] Bearing in mind the results obtained in the rearrangement of several (*Z*)-arylhydrazones of 3-benzoyl-1,2,4-oxadiazole and -isoxazole, this behaviour can be accounted for considering the occurrence in the transition state of a 'catalysis of catalysis'[6] (**10**) in apolar solvents. The occurrence of an amine addition to the N(4)=C(5) double bond of the 1,2,4-oxadiazole ring as indicated in (**11**), which is similar to that proposed by Harsanyi[7] for the rearrangement of some 1,2,4-oxadiazole derivatives, can be discarded.[3i–k] In order to confirm the above reaction mechanism we have studied the rearrangement of (**3f**) in the presence of some pairs of amines (PIP or BuA together with DABCO or TEA). (The apparent pseudo-first-order kinetic constants measured are collected in Table B of a supplementary publication.) In these reactions, in accordance with previous results (see above), no contribution from the term involving only the tertiary amine (TA: *i.e.*, $k'_{II}$[TA]) would be expected, but, because of the lower steric hindrance of DABCO with respect to TEA, a higher effectiveness of DABCO with respect to TEA should be expected. In line



(10)

HA = primary or secondary amine



(11)

with these expectations and considering the pairs of amines used, the apparent first-order kinetic constants fit well equations (6) and (7); as a statistical treatment (stepwise multiple linear

$$k_A = k'_{II}[TA] + k_{II}[PIP] + k_{III}[PIP]^2 + k'_{III}[PIP][TA] \quad (6)$$

$$k_A = k'_{II}[TA] + k_{IV}[BuA]^3 + k'_{IV}[BuA]^2[TA] \quad (7)$$

TA = DABCO or TEA

regression analysis) of the kinetic data has shown [see equations (8)–(10) and related statistical data].

$$10^6 k_A = (0.845 \pm 0.092)[PIP] + (3.52 \pm 0.08)[PIP]^2 + (8.49 \pm 0.09)[PIP][DABCO] \quad (8)$$

($i$ −0.02 ± 0.02, $n$ 21, $r$ 0.9999)

$$10^6 k_A = (1.83 \pm 0.02)[BuA]^3 + (10.0 \pm 0.1)[BuA]^2[DABCO] \quad (9)$$

($i$ −0.01 ± 0.01, $n$ 24, $r$ 0.9997)

$$10^6 k_A = (1.84 \pm 0.01)[BuA]^3 + (0.740 \pm 0.009)[BuA]^2[TEA] \quad (10)$$

($i$ −0.004 ± 0.003, $n$ 23, $r$ 0.9999)

The results of equations (8)–(10) fit our expectations. In fact, (*a*) the terms $k_{II}[PIP]$, $k_{III}[PIP]^2$, and $k_{IV}[BuA]^3$ calculated are practically coincident with those obtained directly by equations (4) and (5) in the presence of the single amine (piperidine or butylamine, respectively); (*b*) the term $k'_{II}[TA]$ is lacking in equations (8)–(10); (*c*) there is no term $k'_{III}[PIP][TA]$ for TA = TEA whereas, in contrast, the term $k'_{III}[PIP][DABCO]$ is significant, confirming the influence of the steric hindrance on general base catalysis[8,3i] [about this point see also (*d*)]; (*d*) the term $k''_{IV}[BuA]^2[TA]$ is significant for both tertiary amines, but the catalytic constant is higher in the presence of DABCO than in the presence of TEA (rate constants ratio *ca.* 13), once more confirming the higher effectiveness of DABCO.

As we have previously pointed out,[3i] the occurrence of mixed terms, including a tertiary amine which does not give any direct contribution to the course of the reaction ($k'_{II}[TA] = 0$), can be accounted for only by a 'catalysis of catalysis' mechanism and not by a mechanism involving the amine addition to the N(4)=C(5) double bond of the 1,2,4-oxadiazole ring.

*Rearrangement of* 3-*Arylureines of* 5-*Phenyl*-1,2,4-*oxadiazole* (**3a–f**) *in DIOX–W* (50:50 *v*:*v*) *in the Presence of Borate Buffers.*—The apparent pseudo-first-order kinetic constants have been measured (see Tables C–H of the supplementary publication) at various temperatures and at variable $pS^+$ ([buffer] 0.0125 mol dm$^{-3}$; see the Experimental section). Because of the lower reactivity of (**3a–f**) with respect to (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (the rate ratios are *ca.* 25 in the $pS^+$-dependent range) it has been also possible to study the reaction at higher $pS^+$ values than with the (*Z*)-arylhydrazones. Kinetic data at 313.15 K have been calculated from activation parameters and some representative plots of log $k_A$ *versus* $pS^+$ are reported in Figure 1. An examination of the plot shows that the reactivity of all the substrates considered presents a limiting rate constant at different $pS^+$ values for each arylureine depending on the nature of the substituent present in the aryl group, which affects the acidity of the hydrogen atom ($N_\alpha$–*H*) of (**3a–f**). The limiting rate constants observed agree with a reaction mechanism occurring through a specific-base catalysis according to reactions (11) and (12). From equations (11) and (12) one can obtain equation (13),

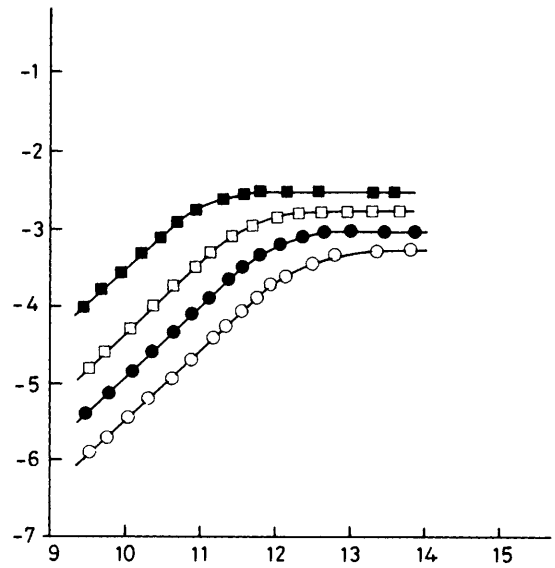


**Figure 1.** Representative plots of log ($k_A$) [○ (**3a**); ● (**3c**); □ (**3e**); ■ (**3f**)] in dioxane–water at 313.15 K *versus* $pS^+$, at total borate buffer concentration 0.125 mol dm$^{-3}$.

$$SH + OH^- \underset{\text{(fast)}}{\overset{K_1}{\rightleftharpoons}} S^- + H_2O \quad (11)$$

$$S^- \xrightarrow[\text{(slow)}]{k_2} \text{products} \quad (12)$$

and for $1 \gg K_1[OH^-]$ or $1 \ll K_1[OH^-]$ equation (13)

$$k_A = K_1 k_2 [OH^-]/(1 + K_1[OH^-]) \quad (13)$$

becomes equations (14) and (15), respectively. At low and high

$$k_A = K_1 k_2 [OH^-] \quad (14)$$

$$k_A = k_2 \quad (15)$$

hydroxide ion concentrations the kinetic behaviour is described by equations (14) and (15), respectively, and apparent pseudo-first-order kinetic constants are observed, which may or may not depend on the $pS^+$ values, as shown in Figure 1.

As a consequence, for each substrate the apparent pseudo-first-order kinetic constants measured at the plateau coincide with the $k_2$ values; on the other hand, the equilibrium constants ($K_1$) can be calculated using equation (14), all the other terms being known, in the range of linear $pS^+$ dependence (for calculated $k_2$ and $K_1$ values, see Table 3). From the inversion

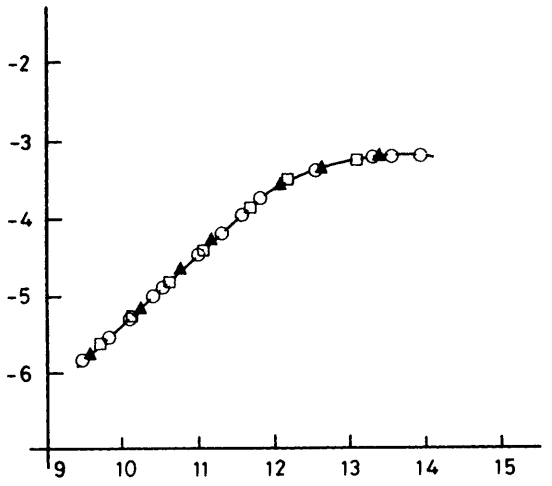
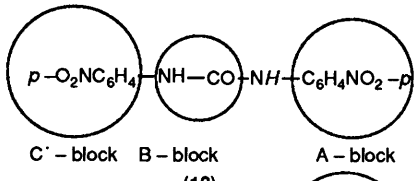



**Figure 2.** Plot of log $(k_A)_{(3b)}$ in dioxane–water at 313.15 K *versus* $pS^+$ at different total borate concentrations: ○, [borate] 0.0125 mol $dm^{-3}$; ▲, [borate] 0.025 mol $dm^{-3}$; □, [borate] 0.050 mol $dm^{-3}$.

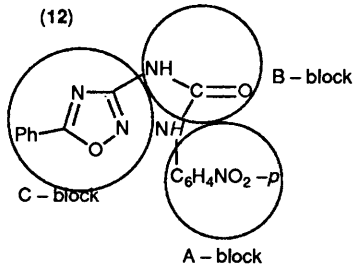
plot relative to the experimental data, similar $k_2$ and $K_1$ values (not reported) can be calculated. The obtained $K_1$ values are related to the corresponding $K_a$ values in DIOX–W [acid dissociation constants relative to $N_\alpha$–*H* of (3)] through equation (16), but it is not easy to measure them directly

$$K_a = K_1 \times 10^{-15.8} \quad (16)$$

because of the rearrangement (3)→(4) occurring at the high $pS^+$ values necessary for these determinations. To overcome this difficulty we have measured the acidity dissociation constant of an arylureine, the *N,N'*-bis(4-nitrophenyl)urea (**12**), which can be considered a good *model* for (**3f**). In fact, the acidity of the $N_\alpha$–*H* in (**3f**) [see formula (**13**)] depends on the electron-withdrawing effects of the *p*-nitrophenyl group (A-block) and of




(12)




(13)

the amido group (B-block), but is little affected by the far 3-(5-phenyl-1,2,4-oxadiazolyl) substituent (C-block). Similarly the acidity of (**12**) depends on the electronic effects of the same A- and B-blocks, the second being little affected by the far *p*-nitrophenyl group (C'-block). On the other hand, the two far C- and C'-blocks (with only a small effect on the acidity constant values) are both electron-withdrawing substituents.

The $K_a$ value of (**12**) has been determined according to Jones and Mueller[9] and the value obtained (corrected for the statistical factor) at 298.15 K (11.68) allows us to calculate a rough $K_1$ value ($1.3 \times 10^4$). This is in agreement with the experimental value ($3 \times 10^4$) calculated for (**3f**).

In order to confirm the nature of the catalysis (specific or general) the rearrangement of (**3b**) at 313.15 K has been studied at two other buffer concentrations (*i.e.* 0.0250 and 0.0500 mol $dm^{-3}$). (The apparent pseudo-first-order kinetic constants measured are collected in Table I of the supplementary publication.) Indeed, if the catalysis is specific, the hydroxide ion, the buffer base, and water can react with the substrate (SH) to give its conjugate base ($S^-$): as long as these reactions are fast enough to maintain the equilibrium between SH and $S^-$, the ratio [SH]/[$S^-$], and therefore the global rate of the reaction will depend only on the proton concentration and not on the buffer concentration. In contrast, if the acid–base equilibria are not fast enough to maintain the equilibrium between SH and $S^-$ and hence the global rate of the reaction will depend on the concentration of each present base (hydroxide ion, buffer, and water), the catalysis will be general. An examination of the plot of Figure 2 (kinetic data are collected in Table I of the supplementary publication) confirms that the catalysis is *specific*.

On the other hand, the $k_2$ and $K_1$ values calculated also agree with the occurrence of specific base catalysis: in fact, the very high $K_1$ values (in all instances $K_1 > 10^3$) and the low $k_2$ values [$(5.5–31) \times 10^{-4}$] confirm that equilibrium (11) is fast and reaction (12) is slow, as required for specific base catalysis. Moreover, the present substituents affect the reactivity; on going from *p*-MeO to *p*-$NO_2$ substituents an increase of reactivity depending on the $pS^+$ has been observed, *i.e.* $(k_a)_{(3f)}/(k_a)_{(3a)}$ *ca.* $10^2$ and 6 have been measured at $pS^+$ 10 and 13.5, respectively. As observed in ACN (see above) the substituent effect cannot be described by a simple Hammett relationship because of some deviations from linearity. Therefore, poor Hammett correlations have been observed (in the $pS^+$ range 9.5–10.5: ρ 1.69 ± 0.33, *n* 6, *r* 0.93; at $pS^+$ 13.5: ρ 0.663 ± 0.102, *n* 6, *r* 0.9556). In contrast, excellent free energy linear plots have been obtained using $\sigma^n$ for (**3a–e**) and $\sigma_p^-$ for (**3f**) (the *p*-nitro group is the only electron-withdrawing substituent used which is able to give a through-resonance effect) in the $pS^+$ range 9.5–10.5 (ρ 1.50 ± 0.03, *i* 0.02 ± 0.02, *n* 6, *r* 0.9994) and at $pS^+$ 13.5 (ρ 0.57 ± 0.02, *i* 0.00 ± 0.01, *n* 6, *r* 0.9984). Since the limiting rate constants appear at different $pS^+$ values, depending on the structure of the arylureine, in the $pS^+$ range 11–13 the corresponding linear free energy correlations are statistically less significant.

Excellent linear free energy relationships can also be obtained considering $k_2$ and $K_1$ values. Obviously, the correlation at $pS^+$ 13.5 coincides with that of $k_2$ (see Figure 1); however, the correlations in the $pS^+$ range 9.5–10.5 are a function of both $k_2$ and $K_1$ [see equation (14)]. Accordingly, an excellent linear free energy plot has been obtained for $K_1$ (ρ 0.97 ± 0.02, *i* 0.01 ± 0.01, *n* 6, *r* 0.9992) using substituent constants as above, and the calculated susceptibility constant agrees with the observation, deriving from equation (14), that at any $pS^+$ in the $pS^+$-dependent range equation (16) must be observed, and since

$$(\rho)_{k_A} = (\rho)_{K_1} + (\rho)_{k_2} \quad (16)$$

ρ values concerning $K_1$ and $k_2$ are both positive, the susceptibility constants calculated are higher in the $pS^+$-dependent than in the $pS^+$-independent range, where they coincide with $(\rho)_{k_2}$. The calculated values of the susceptibility constants agree well with the reaction mechanism indicated. In fact, a higher substituent effect and then a higher susceptibility constant is expected for the equilibrium reaction (which implies the transformation SH ⟶ $S^-$) than for the rearrangement step (which implies the reaction $S^-$ ⟶ $P^-$).

*Activation Parameters.*—The kinetic measurements in DIOX–W have been carried out at various temperatures (range

293–333 K) in order to recalculate $k_A$ from activation parameters. The activation parameters are relevant only in the plateau at high $pS^+$; for each substrate in this range of $pS^+$ these parameters remain unchanged (within the bounds of experimental error) and the reactivity variations, taken as a function of the present substituent are largely entropy-dependent ($\delta\Delta S^{\ddagger}$ *ca.* 35 J $K^{-1}$ $mol^{-1}$). In contrast, the high activation enthalpies show only small variations ($\delta\Delta H^{\ddagger}$ *ca.* 5 kJ $mol^{-1}$). In the $pS^+$-dependent range the activation parameters are of doubtful interpretation because the $k_A$ values, and therefore the activation parameters, are composite values depending upon several reaction processes. However the reactivity variations both for each substrate as a function of $pS^+$ and for all the substrates as a function of the present substituent are again largely entropy-dependent and practically enthalpy-independent.

The activation parameters observed agree with an $S_Ni$-type reaction, with a highly solvated transition state. The formation of this latter is accompanied by a partial loss of the stabilization resonance energy of the 1,2,4-oxadiazole ring, which is only in part balanced by the gain derived from the incipient formation of the new heterocycle (1,2,4-triazolin-5-one). The lower reactivity of arylureines (**3**) with respect to arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole appears essentially enthalpy-dependent ($\delta\Delta H^{\ddagger}$ *ca.* 10 kJ $mol^{-1}$) and is well accounted for by the difference in resonance stabilization between the two rings finally formed (1,2,4-triazolin-5-one and 1,2,4-triazole, respectively).

## Conclusions

The base-catalysed rearrangement of compounds (**3a–f**), *i.e.*, of 1,2,4-oxadiazoles containing an arylureino side chain at C-3, furnishes only the corresponding 1-aryl-3-benzoylamino-1,2,4-triazolin-5-ones (**4a–f**), without any competing formation of 5-arylamino-3-benzoylamino-1,2,4-oxadiazoles (**5**). The reaction mechanism in ACN and in PhH closely resembles that previously observed in the rearrangement of some arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole. However, there is a difference: (**3f**) rearranges in the presence of PIP in PhH also through a pathway requiring only one molecule of amine, probably on account of the acidity of the hydrogen atom ($N_\alpha$–*H*) being higher in the arylureine (**3f**) than in the arylhydrazone (**9**). Moreover a comparison between the extrapolated $k_A$ values for the rearrangement of (**3f**) at [PIP] = 1 mol $dm^{-3}$ and at 313.15 K in ACN ($k_A$ 4.5 × $10^{-2}$ $s^{-1}$) and in PhH ($k_A$ 4.5 × $10^{-6}$ $s^{-1}$) has confirmed the effectiveness of aprotic dipolar solvents with respect to apolar solvents, in favouring mhrs as already shown in the rearrangement of (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole[3h,l] and isoxazole.[2b]

A very interesting difference, for the reaction mechanism in buffered DIOX–W, between the rearrangement of 3-arylureines of 5-phenyl-1,2,4-oxadiazole (**3a–f**) and that of arylhydrazones of 3-benzoyl-1,2,4-oxadiazole has been noticed. For arylureines, limiting rate constants at high $pS^+$ values have been observed and a *specific*-base catalysis has been deduced, at variance with the behaviour of arylhydrazones, for which no limiting rate constants have been observed and *general*-base catalysis is operating. This fact can be related to the acidity of the hydrogen atom ($N_\alpha$–*H*) in arylureines, which readily facilitates equilibrium (11). Therefore, the reaction rate, which shows a limiting value, depends only on the proton concentration. In contrast, in the studied arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, the low acidity of the hydrogen atom [$N_\alpha$–*H* bond, *e.g.*, in (**9**)] means that equilibrium (11) is achieved only slowly and lies well over to the left-hand side, and therefore the reaction rate depends on each base present. The interaction between the substrate and the base gives a transition state which evolves directly to products as in apolar solvents [*e.g.*, see transition state (**7**)].

Under all the experimental conditions used (ACN, PhH, and DIOX–W; amines or buffers) the arylureines (**3**) show rearrangement reactivities which are lower than those of the corresponding arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, indicating that the NCN side chain of 3-arylureines is less effective in promoting the internal nucleophilic substitution characteristic of mhr than the CNN side chain of arylhydrazones of 3-acyl compounds.

Of peculiar interest is the comparison between the behaviour of 3-arylureines of 5-phenyl-1,2,4-oxadiazole and of arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in different solvents. In fact, in ACN and in PhH the two systems react through strictly analogous mechanisms and (notwithstanding the large range of reactivity scanned) by changing the solvent and the amine used, similar rate ratios (*ca.* $10^3$) for the two systems are observed. In contrast, in DIOX–W in the presence of buffers, the two classes of 1,2,4-oxadiazole derivatives follow different reaction pathways, and the high acidity of the hydrogen atom of the $N_\alpha$–*H* bond facilitates the rearrangement, and, in the $pS^+$-dependent range where the comparison is significant, causes lower rate ratios (*ca.* 25) than in ACN and in PhH (*ca.* $10^3$).

## Experimental

M.p.s were determined using a Kofler hot-stage apparatus. IR spectra were determined using a Perkin-Elmer 1310 instrument, UV spectra using a Beckman DU-6 spectrophotometer, and $^1H$ NMR (60 MHz) with a Varian EM 360 A spectrometer (tetramethylsilane used as an internal standard).

*Synthesis and Purification of Compounds.*—Amines,[3i] benzene,[10] dioxane,[10] acetonitrile,[11] (**3b**),[4c] and *N*,*N*′-bis-(4-nitrophenyl)urea[12] were synthesised and/or purified according to the literature methods.

Compounds (**3a, c–f**) were prepared by the reaction between 3-amino-5-phenyl-1,2,4-oxadiazole and the appropriate arylisocyanate. Thus, equimolar amounts of the amino compound and of the isocyanate were melted at 180 °C for 30 min, the crude material worked up with benzene, filtered off, and then purified by crystallisation from ethanol or ethanol–dioxane.

As reported for (**4b**),[4c] to obtain the 1-aryl-3-benzoylamino-1,2,4-triazol-5-ones, compounds (**3a, c–f**) were refluxed (1 h) in ethanol containing an excess of aqueous KOH (10%). Evaporation of the solvent, addition of water and neutralisation with acetic acid gave the rearranged products (**4a, c–f**) which were purified by crystallisation from methanol or methanol–dioxane.

All new compounds gave satisfactory elemental analytical data. Physical data are reported in Table 4.

*pS*$^+$ *and Kinetic Measurements.*—An operational p*H* scale, $pS^+$,[3a,f] was established in aqueous dioxane by employing the $pK_a$ values of acids determined by interpolation from the data reported by Harned and Owen.[13] For DIOX–W (1:1 v/v), the meter reading after calibration against buffers was not significantly different from $pS^+$; in fact it was necessary only to apply a correction of +0.16 to the meter reading.

The kinetics were followed spectrophotometrically by measuring the disappearance of (**3a–f**) as previously described.[3a,h] The wavelengths and log ε values used for spectrophotometric determinations of kinetic constants are reported in Tables A–I

**Table 4.** Physical data of compounds (3) and (4).

| Compd. | M.p./°C | UV[a] $\lambda_{max}$/nm | UV[a] log ε | IR (Nujol)/cm$^{-1}$ $\nu_{NH}$ | IR (Nujol)/cm$^{-1}$ $\nu_{CO}$ | $^1$H NMR δ($CDCl_3$) |
|---|---|---|---|---|---|---|
| **(3a)**[b] | 203–204 | 250 | 4.52 | 3 100, 3 160, 3 220, 3 300 | 1 685 | 3.70 (3 H, s, $OCH_3$), 6.80–8.20 (9 H, m, ArH), 8.90 and 10.10 (2 H, 2 s, NH) |
| **(3b)**[b] | 198–199 | 248 | 4.56 | 3 100, 3 150, 3 220, 3 280 | 1 685 | 6.80–8.20 (10 H, m, 2 Ph), 9.00 and 10.10 (2 H, 2 s, NH) |
| **(3c)**[c] | 211–212 | 250 | 4.60 | 3 130, 3 200, 3 280 | 1 685 | 7.20–8.20 (9 H, m, ArH), 9.20 and 10.20 (2 H, 2 s, NH) |
| **(3d)**[c] | 197–198 | 250 | 4.58 | 3 120, 3 180, 3 250 | 1 670 | 7.00–8.20 (9 H, m, ArH), 9.20 and 10.20 (2 H, 2 s, NH) |
| **(3e)**[d] | 208–209 | 249 | 4.66 | 3 300 | 1 690 | 7.50–8.60 (9 H, m, ArH), 9.50 and 10.30 (2 H, 2 s, NH) |
| **(3f)**[d] | 224–225 | 239 | 4.37 | 3 310, 3 380 | 1 730 | 7.40–8.30 (9 H, m, ArH), 9.60 and 10.30 (2 H, 2 s, NH) |
| **(4a)**[c] | 252–253 | 253 | 4.23 | 3 180, 3 380 | 1 665, 1 690 | 3.70 (3 H, s, $OCH_3$), 6.90–8.10 (9 H, m, ArH), 11.70 (2 H, s, NH) |
| **(4b)**[c] | 250–251 | 256 | 4.17 | 3 280, 3 380 | 1 630, 1 660, 1 690 | 7.00–8.20 (10 H, m, 2 Ph), 11.80 (2 H, s, NH) |
| **(4c)**[c] | 298–299 | 272 | 4.25 | 3 200, 3 380 | 1 650, 1 710 | 7.30–8.20 (9 H, m, ArH), 11.90 (2 H, s, NH) |
| **(4d)**[d] | 242–243 | 274 | 4.24 | 3 120, 3 180, 3 260 | 1 670, 1 700 | 7.00–8.10 (9 H, m, ArH), 11.80 (2 H, br s, NH) |
| **(4e)**[c] | 259–260 | 271 | 4.31 | 3 200, 3 280 | 1 670, 1 710, 1 740 | 7.30–8.80 (9 H, m, ArH), 12.00 (2 H, s, NH) |
| **(4f)**[c] | 320–321 | 339 | 4.23 | 3 120, 3 340 | 1 650, 1 675, 1 715 | 7.50–8.50 (9 H, m, ArH), 12.00 (2 H, br s, NH) |

[a] Wavelengths and log ε at the maximum in dioxane–water (1:1, v/v). [b] Crystallised from ethanol. [c] Crystallised from methanol. [d] Crystallised from dioxane–ethanol.

of the supplementary publication, SUP 56782 (10 pages)* together with the kinetic constants and the activation parameters measured at each p$S^+$ value.

* For details of the Supplementary Publications Scheme see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 2*, Issue 1, p. xvii.

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## References

1 (*a*) M. Ruccia, N. Vivona, and D. Spinelli, *Adv. Heterocycl. Chem.*, 1981, **29**, 141; (*b*) A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc. C*, 1967, 2005; A. S. Afridi, A. R. Katritzky, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1976, 315; A. J. Boulton, 'Lectures in Heterocyclic Chemistry,' Hetero Corporation, Provo, 1973.

2 (*a*) V. Frenna, N. Vivona, G. Macaluso, D. Spinelli, and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1987, 537; (*b*) V. Frenna, S. Buscemi, and C. Arnone, *ibid.*, 1988, 1683.

3 (*a*) D. Spinelli, A. Corrao, V. Frenna, N. Vivona, M. Ruccia, and G. Cusmano, *J. Heterocycl. Chem.*, 1976, **13**, 357; (*b*) D. Spinelli, V. Frenna, A. Corrao, and N. Vivona, *J. Chem. Soc., Perkin Trans. 2*, 1978, 19; (*c*) D. Spinelli, V. Frenna, A. Corrao, N. Vivona, and M. Ruccia, *J. Heterocycl. Chem.*, 1979, **16**, 359; (*d*) V. Frenna, N. Vivona, D. Spinelli, and G. Consiglio, *ibid.*, 1980, **17**, 861; (*e*) *ibid.*, 1981, **18**, 723; (*f*) V. Frenna, N. Vivona, G. Consiglio, A. Corrao, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1325; (*g*) V. Frenna, N. Vivona, A. Corrao, G. Consiglio, and D. Spinelli, *J. Chem. Research*, 1981, (*S*) 308; (*h*) V. Frenna, N. Vivona, G. Consiglio, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1199; (*i*) V. Frenna, N. Vivona, A. Caronia, G. Consiglio, and D. Spinelli, *ibid.*, 1983, 1203; (*j*) V. Frenna, N. Vivona, G. Consiglio, and D. Spinelli, *ibid.*, 1984, 541; (*k*) V. Frenna, N. Vivona, A. Caronia, G. Consiglio, and D. Spinelli, *ibid.*, 1984, 785; (*l*) V. Frenna, N. Vivona, L. Cannella, G. Consiglio, and D. Spinelli, *ibid.*, 1986, 1183.

4 (*a*) Ref. 1(*a*), p. 159; (*b*) W. K. Warburton, *J. Chem. Soc. C*, 1966, 1522; (*c*) M. Ruccia and N. Vivona, *J. Chem. Soc., Chem. Commun.*, 1970, 866; (*d*) M. Ruccia, N. Vivona, and G. Cusmano, *J. Heterocycl. Chem.*, 1971, **8**, 137; (*e*) M. Ruccia, N. Vivona, and G. Cusmano, *J. Chem. Soc., Chem. Commun.*, 1974, 358; (*f*) M. Ruccia, N. Vivona, G. Cusmano, and G. Macaluso, *J. Chem. Soc., Perkin Trans. 1*, 1977, 589; (*g*) N. Vivona, G. Cusmano, and G. Macaluso, *ibid.*, 1977, 1616.

5 O. Schreck, *J. Chem. Educ.*, 1971, **48**, 103; O. Exner, 'Advances in Linear Free Energy Relationships,' 1972, 12 and references therein.

6 J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 833; A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Tetrahedron*, 1975, **31**, 2522.

7 K. Harsanyi, *J. Heterocycl. Chem.*, 1973, **10**, 957.

8 F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, 1963, **85**, 1773; R. P. Bell, M. H. Rand, and K. M. A. Winne-Jones, *Trans. Faraday Soc.*, 1965, **52**, 1093; W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 1966, **88**, 104; T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, 1967, **89**, 2106.

9 L. A. Jones and N. L. Mueller, *J. Org. Chem.*, 1962, **27**, 2356.

10 D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim. (Rome)*, 1965, **55**, 1260.

11 A. Weissberger, 'Techniques of Organic Chemistry,' 2nd ed., Wiley Interscience, New York, 1963, vol. 7, pp. 398 and 435.

12 C. Manuelli and E. Ricca-Rosellini, *Gazz. Chim. Ital.*, 1899, **29**, Part II, 124.

13 H. S. Harned and B. B. Owen, 'The Physical Chemistry of Electrolytic Solution,' ACS Monograph. No. 137, 3rd edn., Reinhold, New York, 1958, pp. 716 and 755.

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