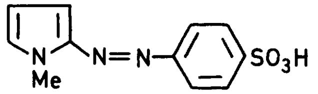
Electrophilic Substitution in Pyrroles. Part 2.[1] Reaction with Diazonium Ions in Acid Solution

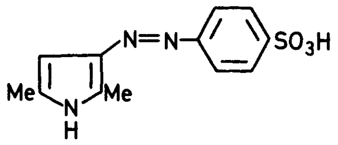
By **Anthony R. Butler,* Peter Pogorzelec, and Peter T. Shepherd,** Department of Chemistry, The University, St. Andrews, Fife

The kinetics of the reactions of five substituted benzenediazonium ions with up to eleven different pyrroles have been examined in detail by stopped-flow spectrophotometry. All the evidence favours attack of the unprotonated pyrrole in an S_E2 mechanism, with a steady-state intermediate. A consideration of two linear free-energy relationships shows that little can be deduced about the nature of any transition state in these reactions. However, protonated pyrrole is a good model for the steady-state intermediate. The activating effects of a methyl group towards electrophilic attack at various positions on the ring have been calculated. The special reactions of 3,4-dimethyl- and 2,3,4,5-tetramethyl-pyrrole are discussed.

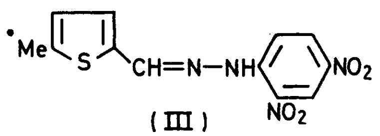
PYRROLES react readily with electrophiles and in Part 1[1] a study of the reaction of pyrrole and various methylpyrroles with 4-dimethylaminobenzaldehyde (Ehrlich's aldehyde) was reported. The data obtained allowed us to calculate the activating effect of a methyl group at various positions on the ring towards electrophilic attack. The success of this study was marred by the imprecise kinetics shown in the reactions of certain methylpyrroles. However, we found that the diazo-coupling of pyrroles is a well behaved reaction and now report a more complete study of structure–reactivity relationships in the pyrrole ring system for this reaction. The study is also directed towards a greater understanding of the van den Bergh method for the determination of bilirubin by reaction with diazotised sulphanilic acid.[2]



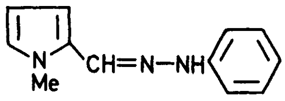
(I)



(II)



(III)



(IV)

RESULTS AND DISCUSSION

Pyrroles react readily with diazonium ions to give highly coloured products and, under acid conditions the product is the monoazo-compound.[3] This has been confirmed in the reactions between diazotised sulphanilic acid and 1-methyl- and 2,5-dimethyl-pyrrole, where the products were identified as (I) and (II). It was found impossible to purify the compounds sufficiently to obtain satisfactory analyses; a similar situation was reported by Kreutzberger and Kalter[4] in the preparation of 4-(2,5-diphenylpyrrol-3-ylazo)benzenesulphonic acid. We feel, however, that the spectral evidence is good enough to characterise (I) and (II), which are the expected products of reaction. Tedder *et al.*[5] have reported that reaction between 2,5-dimethylthiophen and 2,4-dinitrobenzenediazonium tetrafluoroborate results in some coupling through the methyl group to give (III). This compound was readily characterised by the N–H stretching band in the i.r. spectrum. This band was missing in the spectrum of (II) and we conclude that, in the case of this pyrrole compound, there is no reaction at the methyl group. Such a reaction may be peculiar to the very strong electrophile used by Tedder *et al.* An analogous reaction product, (IV), was prepared from 1-methylpyrrole-2-carbaldehyde and found to have the easily identified N–H stretching band (at 3 300 cm^{-1}) for which we had looked in (I) and (II). The α-positions of the pyrrole ring are more susceptible to electrophilic attack than the β-positions[6] and we assume that reaction leads to the 2(5)-azo compound when this is possible. When both α-positions are blocked, then attack occurs at one of the β-positions.

Pyrroles are fairly strong bases and, under the acid conditions used for diazo-coupling, are partially protonated, but we assume that reaction occurs *via* the neutral species. This is anticipated from the work of

---

[1] Part 1, R. S. Alexander and A. R. Butler, *J.C.S. Perkin II*, 1976, 696.

[2] A. A. Hijmans van den Bergh and I. Snapper, *Deut. Arch. Klin. Med.*, 1913, **110**, 540.

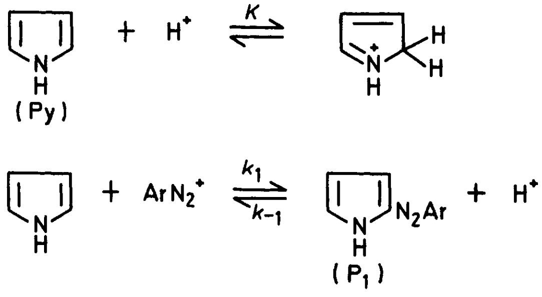
[3] K. Schofield, 'Hetero-aromatic Nitrogen Compounds,' Butterworths, London, 1967, p. 76.

[4] A. Kreutzberger and P. A. Kalter, *J. Org. Chem.*, 1961, **26**, 3790.

[5] S. T. Gore, R. K. Mackie, and J. M. Tedder, *J.C.S. Perkin I*, 1976, 1639.

[6] A. Gossauer, 'Die Chemie der Pyrrole,' Springer–Verlag, Berlin, 1974, p. 105.

Challis and Rzepa[7] on diazo-coupling to indoles. Kinetic evidence, to be described later, shows that diazo-coupling is an equilibrium and so we propose the mechanism shown in Scheme 1. As the products of diazo-coupling reactions are highly coloured the kinetics of reaction were readily studied by stopped-flow spectrophotometry. In all cases the reaction was found to be of the first order in pyrrole and, with an excess of diazonium ion, the rate constant was independent of the initial pyrrole concentration.



SCHEME 1

The reaction scheme is somewhat unusual in that one of the products of reaction, a hydrogen ion, is already present in a large excess as acid conditions were used for preparation of the diazonium compounds. The mathematics of the kinetics of reaction have, therefore, been analysed in detail in the Appendix and from equation (11) it is seen that the experimentally determined rate constant (k_{obs}) is $k_1[ArN_2^+]/(K[H^+] + 1) + k_{-1}[H^+]$. A typical plot of k_{obs} against $[ArN_2^+]$ is shown in Figure 1. That there is an intercept (equal to $k_{-1}[H^+]$) proves that that diazo-coupling is an equilibrium reaction. The values of K, the basicities of the pyrroles, were obtained from the work of Chiang and Whipple.[8] As the acid concentration was, in most cases, low the term $[H^+]$ was taken as the molarity of the acid. In other cases the h_0 value was used;[9] this matter has been discussed in detail previously.[1] The kinetics of reaction of a number of pyrroles with five substituted benzenediazonium ions were examined and the results are given in Table 1.

TABLE 1

Data for the reactions of various pyrroles[a] with $XC_6H_4N_2^+$ ions[b] at 25.0° in acid solution[c]

		p-MeO		H		*p*-SO$_2$OH		*p*-CN		*p*-NO$_2$	
Pyrrole[d]	K/l mol^{-1}	k_1 / l mol^{-1} s^{-1}	k_{-1} / l mol^{-1} s^{-1}	k_1 / l mol^{-1} s^{-1}	k_{-1} / l mol^{-1} s^{-1}	k_1 / l mol^{-1} s^{-1}	k_{-1} / l mol^{-1} s^{-1}	k_1 / l mol^{-1} s^{-1}	k_{-1} / l mol^{-1} s^{-1}	k_1 / l mol^{-1} s^{-1}	k_{-1} / l mol^{-1} s^{-1}
(a) Parent	0.000 16	2.8	0.33	6.8	8.4	23.8	0.60	100	23	220	14
(b) 1-Me	0.000 13	10.9	2.2	25.2	0	68.0	0	287	19	1 000	23
(c) 2,5-Me$_2$	0.195	9.8	0	32.5	0	758	0				
(d) 1,2,5-Me$_3$	0.794	11.8	2.1	24.4	3.2	744	0			1 600	8.6
(e) 2-Me	0.617	129	16	280	154	587	245	3 640	268		
(f) 1,2-Me$_2$	3.15	374	9.2	905	162	1 490	310				
(g) 3,4-Me$_2$	5.00	456	25	869	400	5 270	284				
(h) 2,3-Me$_2$	31.5	142	11	532	398	942	120	7 140	520		
(i) 2,3,5-Me$_3$	100	1.20	0.003 8	1.80	1.1	54	1.54			1 300	0.11
(k) 2,4-Me$_2$	398	6 800	62	13 400	48	26 500	50	63 200	69		
(l) 3-Et-2,4-Me$_2$	3 160	30 500	7.0	177 000	13						

[a] $[Py]_0 = 5 \times 10^{-5}$M. [b] $[XC_6H_5N_2^+] = 0.020$M. [c] [HCl] = 0.05M, except for the 4-nitro-compound, where [HCl] = 0.50M. [d] Designated as in Part 1.

The significance of the values listed will be discussed later.

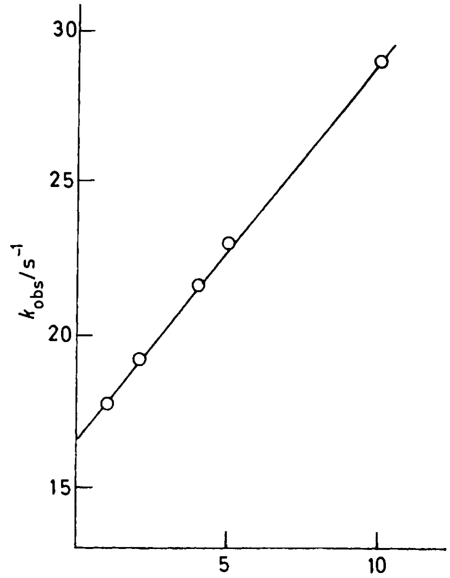


FIGURE 1 Variation of k_{obs} with concentration of 4-sulphobenzenediazonium ions in diazo-coupling with 1,2-dimethylpyrrole at 25°

Confirmation of the proposed reaction scheme comes from a study of the acid dependence of k_{obs}. The results for three pyrroles are shown in Table 2. For the reactions of (b), (d), and (i) k_{-1} is zero so that equation (11) simplifies to $k_{obs} = k_1[ArN_2^+]/(K[H^+] + 1)$. Now, if $K[H^+] \ll 1$, as is the case with (b), then k_{obs} should be independent of the acid concentration. The figures in Table 2, column 2, show that this is approximately correct. The small variation of k_{obs} is due to the non-validity of the approximation at high acid concentrations. Complex formation[10] may also complicate the situation.

[7] B. C. Challis and H. S. Rzepa, *J.C.S. Perkin II*, 1975, 1209.

[8] Y. Chiang and E. B. Whipple, *J. Amer. Chem. Soc.*, 1963, **85**, 2763.

[9] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

[10] S. Koller and H. Zollinger, *Helv. Chim. Acta*, 1970, **53**, 78.

With (d) and (i) the approximation is not valid but, if the scheme is correct, plots of $1/k_{\text{obs}}$ against h_0 should be linear. This is seen to be the case from Figure 2 and so the proposed reaction scheme can be accepted with confidence.

TABLE 2

Variation of k_{obs} with acid concentration for the reaction of 4-sulphobenzenediazonium ions [a] with various pyrroles [b] at 25°

[HCl]/M	(b) $k_{\text{obs}}/\text{s}^{-1}$	(d)	(i)
0.025		5.7	
0.050	0.49	5.8	
0.10	0.68		
0.25	0.79	5.3	0.086
0.50	0.87	4.4	0.067
1.00	0.94	3.1	0.051
1.50	0.79	1.6	0.035
2.00	0.53	1.4	0.033
2.50	0.39	1.0	0.020

[a] 0.020M. [b] *ca.* 5 × 10^{-5}M.

We must now return to a discussion of the figures in Table 1. There is no easily perceived correlation between k_{-1} and K; also the value of the ratio k_1/k_{-1} appears to vary in a random manner. Equally there is no obvious correlation between k_1/k_{-1} and the electrophilicity of the benzenediazonium ion. However, when substitution occurs at an α-position, there is an excellent linear correlation between k_1 and the basicity of the pyrrole (K) covering, in some cases, a range of values of K of 10^7. The only exception to this is 2,3-dimethylpyrrole. A typical plot is shown in Figure 3. Values of k_1 for attack at the β-position fall below this line and may lie on a different curve, but there are too few to be certain of this. The slopes of the curves for α-attack are all *ca.* 0.5.

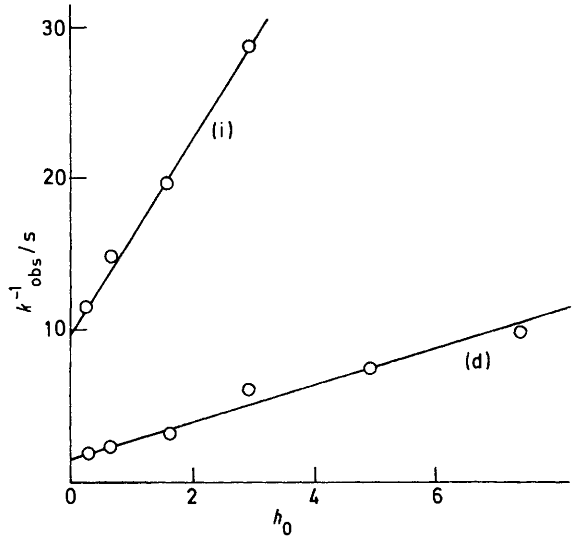


FIGURE 2 Acidity dependence for the diazo-coupling of (d) and (i) with 4-sulphobenzenediazonium ions at 25°

A simple deduction can be made from this Brønsted plot: protonated pyrrole is a good model for the Wheland intermediate formed in the diazo-coupling reaction and this intermediate must be a relatively stable species on the reaction pathway. This matter has been discussed in detail by Zollinger.[11] Details of this part of the reaction are given in Scheme 2. The rate-determining step is proton loss [12] and so the rate of the overall reaction is $k^*[P_2]$. If, as seems most probable, the equilibrium concentration of P_2 parallels the basicity of the pyrrole and, as the overall reaction does this also (the Brønsted plot), k^* must be constant and essentially independent of the pyrrole. This matter will be discussed again later.

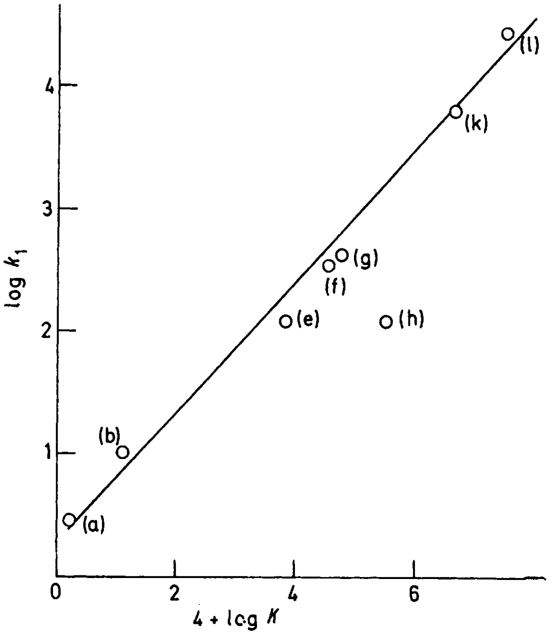
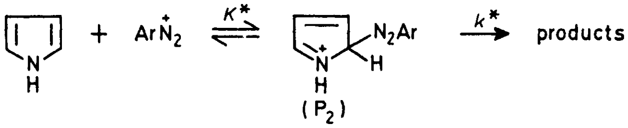


FIGURE 3 Plot of log k_1 against pyrrole basicity for the diazo-coupling of 4-methoxybenzenediazonium ions with various pyrroles



SCHEME 2

From the accumulated data it is possible to plot a series of Hammett plots for pyrroles of different reactivities (Figure 4). Only those reactions involving attack at an α-position have been considered. The ρ values vary over the range 1.2—1.6. Mitsumura *et al.*[13] report larger ρ values (*ca.* 4.3) for the same reaction, but they used only

---

[11] H. Zollinger, 'Azo and Diazo Chemistry Aliphatic and Aromatic Compounds,' Interscience, New York, 1961, pp. 233—238.

[12] R. Ernst, O. A. Stamm, and H. Zollinger, *Helv. Chim. Acta*, 1958, **41**, 2274.

[13] K. Mitsumura, Y. Hashida, S. Skeiguchi, and K. Matsui, *Bull. Chem. Soc. Japan*, 1973, **46**, 1770.

deactivating substituents on the benzenediazonium ion. Different ρ values for electron-attracting and -donating substituents has been reported previously.[14] For a number of diazo-coupling reactions Štěrba and Valter [15] report ρ values ranging from 2.62 to 4.27, so our value is not an unreasonable one.

A value of σ for the 4-sulpho-group is not available. We therefore measured a value from the lowest curve (that for pyrrole) as 0.28 and used this value to obtain points for the remaining four curves. Because of the manner in which these points were obtained, they should be treated with some caution. Hopkinson and Wyatt [16] obtained a σ value of 0.56 for the 3-sulpho-group.

The significant observation from Figure 4 is that, although the substrates vary in reactivity by a factor of 10^4, the value of ρ remains essentially constant. This appears to contradict the selectivity principle, which asserts that a reactive substrate should be less discriminating (exhibit a smaller ρ value) than a less reactive substrate. Olah *et al.*[17] have produced extensive experimental evidence to support the selectivity principle, although this evidence has been criticised by Johnson and Schofield.[18] However, we suggest that if a stable reaction intermediate is formed the selectivity principle does not apply.

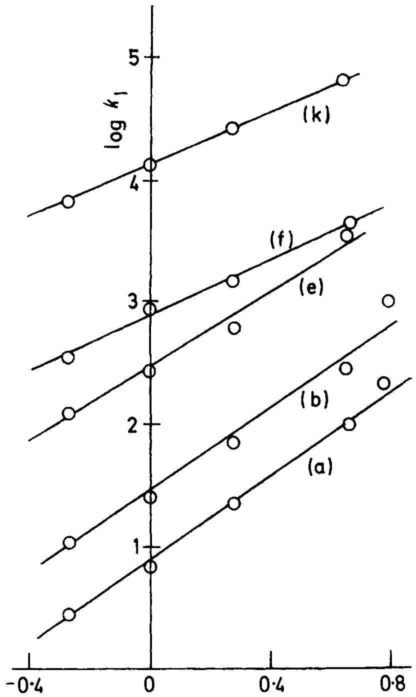


FIGURE 4 Hammett plots for the diazo-coupling of various pyrroles with $XC_6H_4N_2^+$ ions where X is *p*-OMe, H, *p*-SO_2OH, *p*-CN, and *p*-NO_2

It has been shown already that k^* is a constant and so the rate of the overall reaction (*i.e.* formation of P_1) depends upon the equilibrium concentration of P_2. Although 2,4-dimethylpyrrole may be less discriminating in its reactions with substituted benzenediazonium ions than pyrrole, this will not be reflected directly in the equilibrium concentration of P_2. The Brønsted plots show that the concentration of P_2 for each benzenediazonium ion depends on only the basicity of the pyrrole. Clearly the rate of the back reaction (*i.e.* dissociation of P_2) is such that the discriminatory nature of the forward reaction is balanced out. Although this does not necessarily lead to invariant ρ values, it is clear why the selectivity principle does not apply to reactions with a stable reaction intermediate.

The data in Table 1 allow us to calculate the activating effect of a methyl group on different positions on the pyrrole ring. This was done with the data reported in Part I but we now have more results and can obtain a more complete picture of the situation. The calculated effects are given in Table 3. Where comparison is possible, the agreement with our previous results is good. There are too few values to know if the variation of activating effect with electrophilicity, shown by a 5-methyl group, is a genuine effect. The only surprising result is that a 4-methyl group deactivates the 3-position. This is probably a steric effect. A 3-methyl group should also deactivate the 2-position for the same reason, but the effect is masked by the hyperconjugative activating effect.

TABLE 3

Activating effect of a methyl group towards electrophilic attack on the pyrrole ring

Compounds compared	Position of methyl group	Position of attack	Activating effect X = 4-SO_3H	H	4-OMe
(b) and (a)	1	2	2.9	3.7	3.9
(f) and (e)			2.5	3.2	2.9
(e) and (a)	5	2	25	41	47
(f) and (l)			44	72	68
(j) and (e)	3	2	45	48	53
(h) and (e)	4	2	1.6	2.0	1.1
(i) and (c)	4	3	0.03	0.02	0.02

We have assumed that the reaction observed was formation of the monoazo-compounds and, on the stopped-flow time scale, no subsequent reaction was detected. The only exception to this was 3,4-dimethylpyrrole and, in this case, the initially formed intense yellow colour changed to pale blue, a change that was complete within 3 s for reaction with diazotised sulphanilic acid. The rate of disappearance of the yellow species has been determined and the results are shown in Table 4. The small change in k_{obs} as the 4-sulphobenzenediazonium

---

[14] B. Demian, *Tetrahedron Letters*, 1972, 3043.

[15] V. Štěrba and K. Valter, *Coll. Czech. Chem. Comm.*, 1972, **36**, 282.

[16] A. C. Hopkinson and P. A. H. Wyatt, *J. Chem. Soc.* (*B*), 1968, 2526.

[17] G. A. Olah, M. Tashiro, and S. Kobayashi, *J. Amer. Chem. Soc.*, 1970, **92**, 6369; G. A. Olah and S. Kobayashi, *ibid.*, 1971, **93**, 6964; G. A. Olah, *Accounts Chem. Res.*, 1971, **4**, 240.

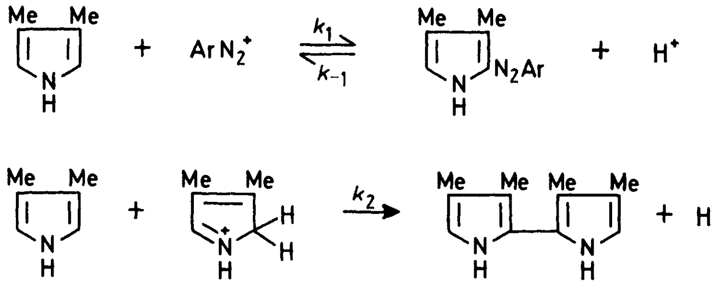
[18] C. D. Johnson and K. Schofield, *J. Amer. Chem. Soc.*, 1973, **95**, 270.

ion concentration was altered indicated that formation of a bisazo-compound did not occur. A possible reaction is that shown in Scheme 3; dimerisation of 3,4-dimethylpyrrole is a known reaction.[19] The kinetics of these reactions are complex but inspection of the Scheme indicates, if we assume that reaction k_2 is much slower than formation of 3,4-dimethylpyrrol-2-ylazobenzene, that fading of the yellow colour will not be greatly influenced by the benzenediazonium ion concentration. As this reaction was not the principle concern of this study, the matter was not investigated further.

TABLE 4

Variation of k_{obs} with benzenediazonium ion concentration for the disappearance of 3,4-dimethylpyrrol-2-ylazobenzene

$10^3[PhN_2^+]/M$	2.0	4.0	5.0	6.1	10
k_{obs}/s^{-1}	0.19	0.17	0.17	0.16	0.16



SCHEME 3

There is reaction between benzenediazonium ions and 2,3,4,5-tetramethylpyrrole and Treibs and Derra-Scherer[20] claim that this is accompanied by elimination of methanol. Over the time scale used in our kinetic experiments we could detect no reaction, except with 4-nitrobenzenediazonium ions. Even in this case, the reaction was at least 1 000 times slower than with pyrroles with a free ring position. T.l.c. of the product of reaction showed that it was a complex mixture, including some tarry material. Tedder *et al.*[5] report that 2,4-dinitrobenzenediazonium ions react with tetramethylthiophen through a methyl group. This diazonium ion also reacts with 2,3,4,5-tetramethylpyrrole in glacial acetic acid to give two coloured products (t.l.c.). The matter was not investigated further, but there may well be attack of methyl group if the ring positions are blocked.

EXPERIMENTAL

Materials.—The preparation of the pyrroles used has been described previously.[1] Amines were recrystallised or distilled before use and converted to benzenediazonium salts by reaction with sodium nitrite and HCl at 0°.

Kinetics.—A ' Canterbury ' stopped-flow spectrophotometer was used. The wavelengths used for the various pyrroles were in the range 420—470 nm. Rate constants were calculated by the method of Kezdy[21] and Swinbourne.[22] Spectra of the coloured products were recorded on a Unicam SP 800 spectrophotometer.

Products.—4-Sulphobenzenediazonium hydrogen sulphate was prepared by the method of Whetsel *et al.*[23] and was coupled[4] with 1-methyl- and 2,5-dimethyl-pyrrole. The products were difficult to purify and no satisfactory analyses were obtained. However, we are confident that the products were (I) and (II) from spectroscopic evidence. In the mass spectra M^+ were 265 and 279 respectively, which are correct for the proposed structures. For (I) the n.m.r. spectrum showed δ(DMSO at 35°) 3.94 (3 H), 6.34 (1 H), 6.76 (2 H), and 7.88 (4 H). For (II) the n.m.r. spectrum showed δ(DMSO at 35°) 2.53 (6 H), 6.54 (1 H), and 7.56 (4 H). Neither (I) nor (II) had an absorption in the region 3 300—3 500 cm^{-1}.

The phenylhydrazone of 1-methylpyrrole-2-carbaldehyde was prepared by the method of Mann and Saunders[24] and formed white crystals, m.p. 124° (lit.,[25] 123°). This compound had the expected strong absorption at 3 300 cm^{-1}.

APPENDIX

The concentration of free pyrrole is given by (1), where

$$[Py] = ([Py]^0_{st} - [P_1])/(K[H^+] + 1) \qquad (1)$$

$[Py]^0_{st}$ is the initial stoicheiometric concentration of pyrrole. The rate of production of P_1 as the reaction approaches equilibrium is given by (2). As ArN_2^+ and H^+ are present

$$d[P_1]/dt = k_1[Py][ArN_2^+] - k_{-1}[P_1][H^+] \qquad (2)$$

in large excesses they are unchanged during the course of the reaction and (2) simplifies to (3). Substitution from (1) gives equation (4) which on rearrangement to (5), can be

$$d[P_1]/dt = k'_1[Py] - k'_{-1}[P_1] \qquad (3)$$

integrated to give (7). At $t = 0$, $[P_1] = 0$ and so the con-

$$\frac{d[P_1]}{dt} = \frac{k'_1([Py])^0_{st} - [P_1])}{(K[H^+] + 1)} - k'_{-1}[P_1] \qquad (4)$$

$$= \frac{k'_1[Py]^0_{st}}{(K[H^+] + 1)} - [P_1]\left(\frac{k'_1}{K[H^+] + 1)} + k'_{-1}\right) \qquad (5)$$

$$= A - B[P_1] \qquad (6)$$

$$- 1/B[\ln (A - B[P_1])] = t + \text{constant} \qquad (7)$$

---

[19] C. O. Bender and R. Bonnet, *J. Chem. Soc.* (*B*), 1968, 2526.

[20] A. Treibs and H. Derra-Scherer, *Annalen*, 1954, **589**, 196.

[21] F. J. Kezdy, J. Jaz, and A. Bruylants, *Bull. Soc. chim. belges*, 1958, **67**, 687.

[22] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.

[23] K. B. Whetsel, G. F. Hawkins, and F. E. Johnson, *J. Amer. Chem. Soc.*, 1956, **78**, 3360.

[24] F. G. Mann and B. C. Saunders, ' Practical Organic Chemistry,' Longman, Green and Co., London, 1952, 3nd edn., p. 177.

[25] F. Alessandri, *Atti della Reale Academia dei Lincei*, 1915, **24**, 198.

stant of integration is $-1/B[\ln A]$ and the full integrated equation is (8). This may be simplified by setting the

$$-1/B[\ln (A - B[P_1])] = t - 1/B[\ln A] \qquad (8)$$

equilibrium condition that at $[P_1]_e$, $d[P_1]/dt = 0$, where $[P_1]_e$ is the final or equilibrium concentration of product. Applying this to (6) we obtain (9). Substitution in (8) gives

$$A = B[P_1]_e \qquad (9)$$

(10), which may be rearranged to (11). Therefore, the slope

$$-1/B[\ln (B[P_1]_e - B[P_1])] = t - 1/B[\ln A] \qquad (10)$$

$$-\ln ([P_1]_e - [P_1]) = Bt + \ln B/A \qquad (11)$$

of a plot of $-\ln([P_1]_e - [P_1])$ against t (*i.e.* k_{obs}) is $k_1[ArN_2^+]/(K[H^+] + 1) + k_{-1}[H^+]$.

[6/2170 *Received, 24th November,* 1976]