The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XXXV.[1] The Nitration of Phenylpyrazolones

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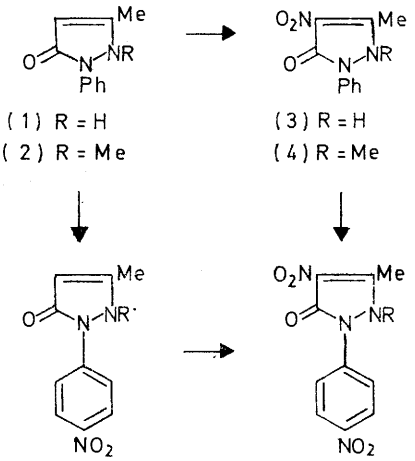
Nitration at the 4-position of 3-methyl-1-*p*-nitrophenyl-5-pyrazolone and its *N*- and *O*-methyl derivatives and at the *para*-position of 3-methyl-4-nitro-1-phenyl-5-pyrazolone and its *N*- and *O*-methyl derivatives has been studied. All the compounds react as the conjugate acid at high acidities, but some undergo a mechanistic changeover to nitration *via* the free base at low acidity. The nitration rates are compared within the series studied and with those of other heteroaromatic compounds.

THE nitration of carbonyl derivatives of five-membered heterocycles (azolones) has not been studied mechanistically although such reactions have long been used preparatively. We have extended our studies of the nitration of pyridones [2] and of azoles,[3] to azolones, and we now report on some pyrazolone derivatives. Pyrazolone chemistry was developed extensively around the turn of the century as a result of the antipyretic activity discovered for antipyrine (2).

Some electrophilic substitution reactions of 1-phenyl-5-pyrazolones have been reported: the first nitration appears to occur preferentially either in the 4-position,[4,5] or in the *para*-position [6] and further nitration gives the 4,*p*-dinitro-derivatives.[7] Sulphonation occurs at the 4-position.[8] The action of bromine on 1-phenyl-5-pyrazolones introduces first one and then a second bromine atom into the 4-position before reaction occurs in the phenyl ring.[9-11] Chlorination under a variety of conditions [9,12] also yields the 4,4-dichloro-derivatives.

In view of the susceptibility of 1-phenyl-5-pyrazolones to nitration at both the 4-position and the *para*-position of the phenyl ring, we have now studied the second nitration of the 4- (3) and of the *p*-mononitro-derivative (5) of 3-methyl-1-phenyl-5-pyrazolone. 1-Substituted 5-pyrazolones are tautomeric with three contributary



(1) R = H
(2) R = Me
(3) R = H
(4) R = Me
(5) R = H
(6) R = Me
(7) R = H
(8) R = Me

forms (9a—c); [13] we have included in our study the *N*-methyl compounds (4) and (6) [as models for the tautomeric form (9a)] and the methoxy-derivatives (11) and

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[11] G. Westöö, *Acta Chem. Scand.*, 1952, **6**, 1499.
[12] L. Knorr and P. Duden, *Ber.*, 1892, **25**, 766 (Note 1).
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(12) [as models for (9b)]. Attempts to nitrate quaternised derivatives as (14) failed.

Preparation of Compounds.—Compounds of the 4-nitro-series were prepared by direct nitration, using amyl nitrite for the conversion (1) ⟶ (3),[5] and nitric acid for the conversions (2) ⟶ (4),[4] and (10) ⟶ (11): compound (11) was characterised by its n.m.r. spectrum (Table 1). In the 1-*p*-nitrophenyl series, compound (5) was previously prepared by ring closure;[6] we found that it resulted from the treatment of (1) with one mole of nitric acid in sulphuric acid (*cf.* ref. 14). Methylation of (5) with dimethyl sulphate and sodium hydroxide gave (6), whereas methylation of (5) with diazomethane gave (12).

Nitration in mixed acid of (1), (3), and (5) gave in each case the same dinitro-derivative (7) (Table 2). Similarly, (2), (4), and (6) each gave (8); further, (10)—(12) each gave (13) (Table 2). The n.m.r. spectra of each of the crude dinitro-products were examined in an attempt to determine the amounts of 1-*o*-nitrophenyl and 1-*m*-nitrophenyl compounds present: in each case no signals directly attributable to *ortho*- and *meta*-isomers could be detected, and we believe that the proportion of these isomers is <5% in all cases. This conclusion is supported by the m.p.s of the crude nitration products which were close to those of the pure isomers (see Experimental section) in each case.

TABLE 1

^{1}H N.m.r. chemical shifts (τ [a]) and coupling constants (Hz) at 60 MHz of substituted 5-pyrazolones and 5-methoxypyrazoles in CF_3CO_2H

	Pyrazole ring position									
	1			2			4		5	
Compound	Subst.	τ	J [b]	Subst.	τ	3-Me	Subst.	τ	Subst.	τ
(1) [c]	Ph	2·34				7·45	H	3·84	(O)	
(2)	Ph	2·35		Me	6·47	7·46	H	3·89	(O)	
(3)	Ph	2·48				7·05	(NO_2)		(O)	
(4)	Ph	2·25		Me	6·23	7·03	(NO_2)		(O)	
(5)	*p*-$C_6H_4NO_2$	1·40, 2·0	9·0			7·38	H	3·75	(O)	
(6)	*p*-$C_6H_4NO_2$	1·48, 2·01	9·3	Me	6·23	7·35	H	3·68	(O)	
(7)	*p*-$C_6H_4NO_2$	1·35, 1·90	8·7			7·05	(NO_2)		(O)	
(8)	*p*-$C_6H_4NO_2$	1·41, 2·05	7·9	Me	6·22	7·03	(NO_2)		(O)	
(10) [d]	Ph	2·80				8·30	H	5·09	OMe	6·69
(11)	Ph	2·34				7·19	(NO_2)		OMe	5·72
(12)	*p*-$C_6H_4NO_2$	1·5, 2·10	9·0			7·35	H	3·72	OMe	5·75
(13)	*p*-$C_6H_4NO_2$	1·5, 2·10	8·9			7·26	(NO_2)		OMe	5·70

[a] Relative to internal Me_4Si = 10 for solutions in CF_3CO_2H or $CDCl_3$; for H_2SO_4 TMAS = 6·80. [b] Coupling constants (Hz) for *p*-nitrophenyl substituents. [c] H_2SO_4 as solvent. [d] $CDCl_3$ as solvent.

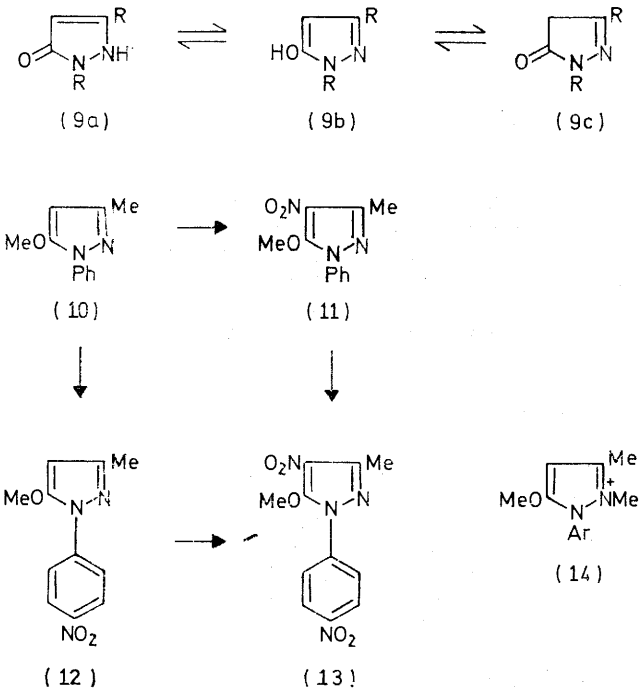

TABLE 2

Preparative nitrations

	Prepared by further nitration of 4-nitro-compound				Prepared by further nitration of 1-*p*-nitrophenyl compound		
Nitration product	Starting material	Yield (%)	Crude m.p. (°C)		Starting material	Yield (%)	Crude m.p. (°C)
(7)	(3)	92	208—212		(5)	84	193—198
(8)	(4)	90	276—280		(6)	92	278—282
(13)	(11)	86	175—180		(12)	94	178—182

EXPERIMENTAL

Materials.—The following were prepared by the literature methods quoted: 3-methyl-1-phenyl-, m.p. 131—133° (lit.,[15] m.p. 127°); 3-methyl-4-nitro-1-phenyl-, m.p. 128° (from acetic acid) (lit.,[5] m.p. 127°) (Found: C, 54·6; H, 4·1; N, 19·2. Calc. for $C_{10}H_9N_3O_3$: C, 54·8; H, 4·2; N, 19·2%); 2,3-dimethyl-1-phenyl, m.p. 113—113·5° (lit.,[16] m.p. 113°); 2,3-dimethyl-4-nitro-1-phenyl-, yellow needles, m.p. 288—289° (from acetic acid) (lit.,[4] m.p. 273°) (Found: C, 56·3; H, 4·8; N, 18·2. Calc. for $C_{11}H_{11}N_3O_3$: C, 56·6; H, 4·7; N, 18·0%); 2,3-dimethyl-4-nitro-1-*p*-nitrophenyl-Δ^3-pyrazolin-5-one, yellow needles, m.p. 280—282° (from acetic acid)

[14] G.P. 61,794 (' Beilsteins Handbuch der Organischen Chemie,' eds. B. Prager and P. Jacobson, Springer Verlag, Berlin, 1936, vol. 24, p. 24).

[15] L. Knorr, *Ber.*, 1883, **16**, 2597.

[16] L. Knorr, *Annalen*, 1887, **238**, 203.

(lit.,[17] m.p. 276°) (Found: C, 47·5; H, 3·6; N, 20·4. Calc. for $C_{11}H_{10}N_4O_5$: C, 47·5; H, 3·6; N, 20·1%); 5-methoxy-3-methyl-1-phenylpyrazole, b.p. 162° at 3·7 mmHg (lit.,[18] b.p. 239—240° at 212 mmHg) (Found: C, 70·5; H, 6·3; N, 14·6. Calc. for $C_{11}H_{12}N_2O_7$: C, 70·2; H, 6·4; N, 14·9%).

3-Methyl-1-p-nitrophenyl-5-pyrazolone.—Nitric acid (*d* 1·45; 1·03 g) and sulphuric acid (*d* 1·84; 10 ml) were added to 3-methyl-1-phenyl-5-pyrazolone (2 g) in sulphuric acid (10 ml) at 0°. After 10 h at 20°, the mixture was added to ice (100 g) to give the nitro-derivative (2·1 g, 90%) which crystallised from acetic acid as needles, m.p. 218° (lit.,[6] m.p. 218°) (Found: C, 54·7; H, 4·3; N, 18·9. Calc. for $C_{10}H_9N_3O_3$: C, 54·8; H, 4·1; N, 19·1%).

3-Methyl-4-nitro-1-p-nitrophenyl-5-pyrazolone.— Nitric acid (*d* 1·42; 2·1 g) and sulphuric acid (*d* 1·84; 10 ml) were added to 3-methyl-1-phenyl-5-pyrazolone at 0°. After 12 h at 20° the mixture was poured onto ice (100 g) to give the *dinitro-derivative* (2·3 g, 72%) which separated from ethanol as brown needles, m.p. 212° (Found: C, 45·1; H, 3·2; N, 20·7. $C_{10}H_8N_4O_5$ requires C, 45·3; H, 3·1; N, 21·0%).

2,3-Dimethyl-1-p-nitrophenyl-Δ³-pyrazolin-5-one.— 3-Methyl-1-*p*-nitrophenyl-5-pyrazolone (2·9 g), sodium hydroxide (0·53 g), water (10 ml), and dimethyl sulphate (1·15 g) were heated for 1 h at 100°. The dimethyl derivative (1·5 g, 50%) separated on cooling: it crystallised from ethanol as yellow needles, m.p. 138—139° (Found: C, 56·5; H, 4·7; N, 18·1. $C_{11}H_{11}N_3O_3$ requires C, 56·6; H, 4·7; N, 18·0%).

5-Methoxy-3-methyl-1-p-nitrophenylpyrazole.—3-Methyl-1-*p*-nitrophenyl-5-pyrazolone (1 g) was added to ethereal diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (1·5 g) as in ref. 19]. After 12 h at 20° the *methoxy-compound* (0·72 g, 65%) separated: it crystallised from ethanol (charcoal) as pale yellow needles, m.p. 144—145° (Found: C, 56·6; H, 5·1; N, 18·0. $C_{11}H_{12}N_3O_3$ requires C, 56·4; H, 5·1; N, 18·0%).

5-Methoxy-3-methyl-4-nitro-1-phenylpyrazole.—Nitric acid (*d* 1·42; 4 ml) was added dropwise at 0° to 5-methoxy-3-methyl-1-phenylpyrazole (1 g). The mixture was heated for 3 h at 40° and poured onto ice (50 g). The *4-nitro-compound* (0·9 g, 70%) separated: it crystallised from ethanol (charcoal) as pale yellow needles, m.p. 94—95° (Found: C, 56·6; H, 4·8; N, 18·4. $C_{11}H_{12}N_3O_3$ requires C, 56·6; H, 4·7; N, 18·0%).

5-Methoxy-3-methyl-4-nitro-1-p-nitrophenylpyrazole.—Premixed nitric acid (*d* 1·42; 0·32 g) and sulphuric acid (*d* 1·84; 5 ml) were added dropwise at 0° to 5-methoxy-3-methyl-1-phenylpyrazole (1 g) in sulphuric acid (5 ml). The mixture was set aside for 2 h at 20°, and then poured onto ice (50 g). The *dinitro-compound* (1·1 g, 80%) separated: it crystallised from ethanol (charcoal) as yellow needles, m.p. 182—183° (Found: C, 47·6; H, 3·7; N, 19·6. $C_{11}H_{10}N_4O_5$ requires C, 47·5; H, 3·6; N, 20·1%).

5-Methoxy-2,3-dimethyl-1-phenylpyrazolium Perchlorate.—3-Methyl-1-phenyl-5-pyrazolone (1 g) and methyl trifluoromethanesulphonate (0·2 g) were dissolved in ethanol and heated for 2 h. Addition of sodium perchlorate (1 g) gave the *perchlorate* which recrystallised from water as needles, m.p. 124—125° (Found: C, 47·7; H, 5·1; N, 9·4. $C_{12}H_{15}ClN_2O_5$ requires C, 47·6; H, 5·0; N, 9·3%).

TABLE 3

U.v. and pK_a data for substituted pyrazoles

Compound	Substituent 1	2	3	4	5	$\lambda_{max.}$/nm (log ε) Neutral species	Cationic species	λ/nm [a]	Proton addition λ/nm [b]	H_0 [‡]	*m*	pK_a
(1)	Ph	H	Me	H	O	233 (4·14)	238 (4·06)					1·42 [c]
(2)	Ph	Me	Me	H	O	243 (3·96)	225 (4·05)		255	1·52	1·0	1·52
						257 (3·94)						1·40 [c]
(3)	Ph	H	Me	NO_2	O	245 (4·19)	260 (4·03)	315	245	−4·08	0·44	−1·8
(4)	Ph	Me	Me	NO_2	O	330 (3·91)	278 (3·94)	270	275	−3·06	0·62	−1·9
(5)	*p*-$C_6H_4NO_2$	H	Me	H	O	285 (3·74)	295 (4·01)	265			0·5 [d]	0·5 [d]
(6)	*p*-$C_6H_4NO_2$	Me	Me	H	O	287 (4·17)	300 (4·14)	260			0·5 [d]	0·5 [d]
(7)	*p*-$C_6H_4NO_2$	H	Me	NO_2	O	320 (4·04)	315 (3·96)		285	−6·05	0·36	−2·2
(8)	*p*-$C_6H_4NO_2$	Me	Me	NO_2	O	225 (4·17)	270 (4·24)		325	−4·10	0·54	−2·2
(10)	Ph		Me	H	MeO	285 (4·01)	295 (4·2)					+2·34 [e]
(11)	Ph		Me	NO_2	MeO	290 (4·01)	255 (4·2)	(290)	252	−2·78	0·58	−1·6
(12)	*p*-$C_6H_4NO_2$		Me	H	MeO	287 (4·12)	299 (4·16)	(275)	317	−7·02	0·35	−2·5
(13)	*p*-$C_6H_4NO_2$		Me	NO_2	MeO	*f*	290 (4·72)		272	−2·85	0·73	−2·1
							275 (4·27)					

[a] λ for nitration. [b] λ for pK_a. [c] Taken from ref. 13. [d] Estimated values, see text. [e] Value for 5-ethoxy-3-methyl-1-phenylpyrazole, taken from ref. 13. [f] log ε Value for this compound could not be determined owing to rapid decomposition in 0·1N-NaOH and in water.

Spectroscopy.—N.m.r. spectra were recorded at 100 MHz (Varian HA100) or at 60 MHz (Perkin Elmer R12) with sample spinning: Me_4Si was used throughout as an internal standard. U.v. spectra were determined on a Unicam SP 800 recording spectrophotometer; individual values of maximum ε and kinetic and basicity determinations utilised a manual SP 500 instrument. pK_a Values (Table 3) were measured by the spectrophotometric procedure.[20]

Kinetic Determinations.—Nitric and sulphuric acids were AnalaR grade. H_0 Values [21] and H_R values [22a] were taken from the scales recently established in one of our laboratories and were corrected for temperature variation.

Nitrations were followed kinetically in u.v. cells by measuring the increased absorption of the dinitro-compound (as cation). Compounds (4), (5), (6), and (12) were followed throughout the acidity range under pseudo-first-order conditions with a molar ratio of nitric acid : substrate of *ca.* 30 : 1.

[17] A. Michaelis, *Annalen*, 1911, **378**, 333.
[18] H. v. Pechmann, *Ber.*, 1895, **28**, 1624.
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[22] (*a*) N. L. Dassanayake, C. D. Johnson, A. R. Katritzky, and T. W. Toone, submitted to *J. Amer. Chem. Soc.*; (*b*) R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.

TABLE 4

Nitration of substituted pyrazoles in the high and low acidity regions

H_2SO_4 (%)	$-H_0$ [a]	$-(H_R + \log a_{H_2O})$ [b]	$-\log k_2$(obs)	$\log k_2$(fb)	$\log k_2$* [c]
3-Methyl-4-nitro-1-phenyl-5-pyrazolone (3) (25°)					
77·51	7·03	15·42	−0·511		4·69
76·25	6·81	14·96	−0·114		4·76
73·59	6·39	14·06	0·709		4·82
71·90	6·10	13·50	1·338		4·76
2,3-Dimethyl-4-nitro-1-phenyl-Δ^3-pyrazolin-5-one (4) (25°)					
98·11	10·45		2·234		
95·75	9·93		2·178		
93·92	9·64	22·02	1·987		−1·99
90·54	9·07	20·57	1·661		−1·70
88·63	8·83	19·82	1·701		−1·49
85·71	8·37	18·66	1·930	1·360	−0·89
83·88	8·13	17·95	2·020	1·120	−0·35
80·76	7·58	16·66	2·550	0·250	0·40
79·63	7·40	16·17	2·710	−0·020	0·74
77·50	7·03	15·38	3·030	−0·570	1·19
75·40	6·68	14·68	3·270	−1·030	1·65
3-Methyl-1-*p*-nitrophenyl-5-pyrazolone (5) (40°)					
96·12	9·67		−0·028		
94·43	9·38		−0·151		
92·29	9·05	20·18	−0·303		+0·401
88·84	8·52	18·90	−0·600		+1·38
87·14	8·32	18·30	−0·520		+1·88
85·93	8·10	17·92	−0·240	4·790	+1·97
84·51	7·86	17·34	−0·115	4·540	+2·40
83·46	7·67	16·92	0·160	4·175	+2·54
82·52	7·52	16·47	0·303	3·957	+2·85
81·10	7·25	15·82	0·599	3·526	3·18
80·03	7·08	15·15	0·712	3·328	3·74
76·51	6·56	14·26	1·240	2·540	4·11
73·62	6·13	13·46	1·672	1·893	4·47
2,3-Dimethyl-1-*p*-nitrophenyl-Δ^3-pyrazolin-5-one (6) (25°)					
95·13	9·84		1·860		
94·65	9·77	22·33	1·807		−1·81
91·18	9·20	20·82	1·654		−1·62
89·59	8·91	20·20	1·522		−1·44
87·73	8·67	19·46	1·777		−1·39
85·98	8·49	18·67	1·932	2·813	−0·95
84·03	8·13	17·95	2·636	1·929	−0·99
83·94	8·12	17·90	2·788	1·772	−1·17
82·39	7·85	17·28	2·852	1·573	−0·50
81·59	7·70	16·98	3·148	1·202	−0·53
80·01	7·45	16·33	3·298	0·927	−0·02
76·71	6·91	15·01	3·948	0·007	+0·65
5-Methoxy-3-methyl-4-nitro-1-phenylpyrazole (11) (25°)					
95·46	9·87		0·474		
93·81	9·62		0·445		
91·10	9·17		0·325		
89·68	8·94	20·21	0·294		−0·19
87·82	8·68	19·49	0·372		−0·01
86·92	8·53	19·14	0·777		−0·19
84·66	8·22	18·22	1·284		+0·14
81·40	7·68	16·91	1·940		+0·75
81·73 [d]	7·16	15·32	0·880		+2·92
79·88 [d]	6·90	14·43	1·550		+3·57
78·00 [d]	6·62	13·74	2·390		+3·09
76·00 [d]	6·30	13·16	3·120		+3·13
5-Methoxy-3-methyl-1-*p*-nitrophenylpyrazole (12) (40°)					
98·48	10·25		1·584		
95·47	9·56		1·420		
93·09	9·18		1·187		
89·64	8·63	19·20	0·963		−0·41
87·77	8·36	18·51	1·341		−0·21
86·09	8·11	17·99	1·764		−0·07
84·45	7·83	17·46	2·088		+0·26
83·20	7·63	16·81	2·520		+0·28
81·93	7·40	16·19	2·869		+0·53
81·61	7·35	16·05	2·925		+0·63
80·93	7·13	15·49	3·583		+0·32

[a] H_0 Values are corrected [21] for temperature. [b] H_R Values and log a_{H_2O} are corrected [22,24] for temperature. [c] No correction was made for the half-protonation point of HNO_3, at elevated temperatures. [d] Carried out at 50 °C.

Compound (11) was followed at lower acidities under psuedo-first-order conditions but in the range 84—98% acid under second-order conditions. Compound (3) was followed under psuedo-first-order conditions at low acidities; at high acidities it reacted too quickly for convenient measurement. Substrates were also heated in sulphuric acid under conditions as for nitration except for the absence of nitric acid: all were unchanged (u.v. spectrum).

All rate constants (Tables 4 and 5) were calculated using calculated infinity optical densities derived from the known extinction coefficient: for each compound these infinity optical densities agreed with those measured to within 4%. Rate constants are defined by equations (1)—(3), and are expressed throughout in l mol^{-1} s^{-1}. In these equations

TABLE 5

Dependence of rate of nitration on temperature

In 84·1% H_2SO_4			In 91·17% H_2SO_4	
T(°C)	$-\log k_2$(obs)	$\log k_2$(fb) [a]	T(°C)	$-\log k_2$(obs)
2,3-Dimethyl-4-nitro-1-phenyl-Δ^3-pyrazolin-5-one				
24·4	2·125	1·009	24·4	1·876
25·5	1·971	1·163	33·0	1·467
33·2	1·690	1·357	44·5	1·226
44·5	1·317	1·600	53·5	0·971
2,3-Dimethyl-1-*p*-nitrophenyl-Δ^3-pyrazolin-5-one				
30·3	2·046	2·469	25·0	1·653
35·3	1·786	2·684	33·0	1·506
40·2	1·616	2·809	44·5	1·172
42·3	1·556	2·854	52·5	1·101
3-Methyl-1-*p*-nitrophenyl-5-pyrazolone				
In 96·18% H_2SO_4				
24·0	0·488			
30·0	0·312			
36·0	0·170			
40·0	0·048			

[a] Calculated using equation (2).

k_2(obs) is the observed second-order rate constant, k_2(fb) is the second-order rate constant corrected for the concentration of free base, k_2* is the second-order rate constant corrected for the concentration of NO_2^+ (see ref. 2). The H_0 values of half protonation and the slopes of $-\mathrm{d}(\log[BH^+]/[B])/\mathrm{d}H_0$ are denoted by $H_0^{\frac{1}{2}}$ and m respectively.[20,21]

$$-\mathrm{d}[\text{substr.}]/\mathrm{d}t = k_2(\text{obs})\,[\text{substr.}][HNO_3]_{\text{stoich}} \quad (1)$$

$$\log k_2(\text{fb})_T = \log k_2(\text{obs})_T + m(H_0^{\frac{1}{2}} - H_0)_T \quad (2)$$

$$\log k_2^* = \log k_2(\text{obs}) - \log\{[NO_2^+]/[HNO_3]_{\text{stoich}}\} \quad (3)$$

RESULTS AND DISCUSSION

pK_a *Values.*—The *p*-nitrophenylpyrazolones (5) and (6) show u.v. spectra which are similar for free base and cation. Their pK_a values could not be determined by the ^{1}H n.m.r. method due to low solubility in aqueous media. By comparison of the effects on the basicity in the 4-nitro-1-phenyl-5-pyrazolone series of a further nitro-group in the *para*-position, we estimate that the H_0 for half protonation of (5) and (6) will be $+0{\cdot}5 \pm 0{\cdot}5$. The acidity function followed will be similar to the other compounds (see Table 3) and we take m as 0·5 for both (5) and (6).

Mechanism of the Nitrations.—Plots of log k_2(obs) against $(H_R + \log a_{H_2O})$ yield good straight lines (Figure 1). For three of the compounds [(3), (11), and (12)] the slopes (Table 6) are close to unity, indicating majority species (*i.e.* conjugate acid) nitration.[22b] The other three compounds [(4)—(6)] show considerably lower slopes, indicating free base nitration; where a concentration correction is made for the free base content the corrected slopes for these three compounds (4)—(6) become larger, supporting the conclusion that they undergo nitration as free bases.

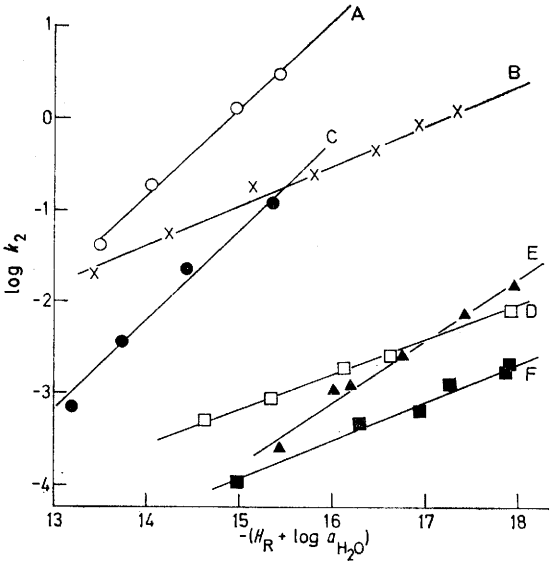


FIGURE 1 The Moodie–Schofield plots for nitration of phenylpyrazolones: A, ○, (3); B, ×, (5); C, ●, (11); D, □, (4); E, ▲, (12); F, ■, (6)

Five of the compounds were also studied at high acidity but the rate for 3-methyl-4-nitro-1-phenyl-5-pyrazolone (3) was too fast for convenient measurement. All the compounds measured showed d [log k_2(obs)]/dH_0 slopes in the range 0·22—0·53, over the region H_0 −9 to −10, which is typical for nitration as majority species, *i.e.* as conjugate acids,[23,24] see Figure 2.

The modified rate profiles, log k_2* *vs.* H_0 (Figure 3), provide an alternative criterion for the reaction mechanism.[2] For compounds (3), (11), and (12), relatively small slopes indicate the conjugate acid mechanism throughout. Compound (5) gives an inclined line which suggests a free base mechanism at acidities lower than H_0 — 8·4. Figure 3 shows clearly the mechanistic changeover from free base at low acidity to conjugate acid at high acidity for compounds (4) and (6).

Arrhenius parameters afford some confirmatory evidence for the mechanism assigned. For conjugate acid mechanisms, values of $\Delta H^{\ddagger}$ of *ca.* 8—14 kcal mol^{-1} are frequently observed [24] indicating (Table 7) that compounds (4) and (6) undergo nitration as the free base species at low acidities, but that (4)—(6) are all nitrated as conjugate acids at high acidity.

Relative Nitration Rates at the para*-Position of a*

[23] E. F. V. Scriven, Ph.D. Thesis, University of East Anglia, 1969.

[24] A. G. Burton, Ph.D. Thesis, University of East Anglia, 1971.

1-*Phenyl Ring*.—Δ^3-Pyrazolin-5-ones are protonated at the oxygen atom.[13] Hence, compounds (3), (4), and (11) form cations of similar structures, (15)—(17), respectively. In the high acidity region all these compounds undergo nitration as the cations, but the rates differ considerably in the sense (15) ≫ (17) > (16). We believe that the differences observed reflect the steric hindrance to conjugation between the two rings: the conjugation will be severely impeded by the *N*-methyl group in (16) and impeded to a lesser extent by the *O*-methyl group in (17). Replacement of OH or NH by OMe or NMe will also decrease hydrogen bonding to the

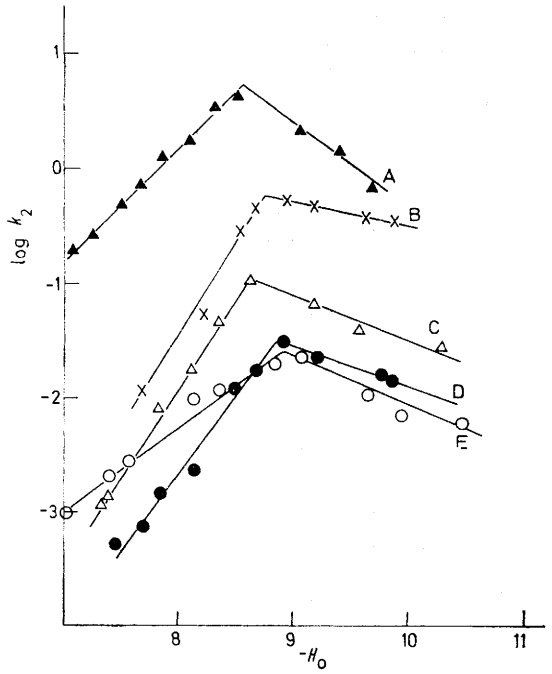


FIGURE 2 The high acidity rate profiles for nitration of phenyl pyrazolones: A, ▲, (5) at 40°; B, ×, (11) at 25°; C, △, (12) at 40°; D, ●, (6) at 25°; E, ○, (4) at 25°

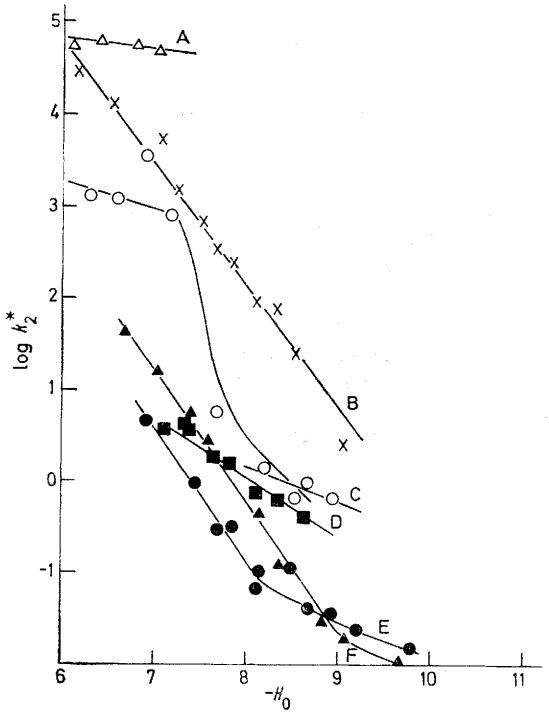


FIGURE 3 Tarhan plots for nitration of substituted pyrazoles: A, △, (3) at 25°; B, ×, (5) at 40°; C, ○, (11) at 25°; D, ■, (12) at 40°; E, ●, (6) at 25°; F, ▲, (4) at 25°

TABLE 6

Rate profile slopes for nitration of 3-methyl-1-phenylpyrazoles and 3-methyl-1-phenyl-5-pyrazolones

Compound	Ring substituent(s)		Position of nitration	Low acidity reegion					High acidity region 92—98% H_2SO_4		
				T(°C)	Slope [a]	Corr. coeff.	Slope [b]	Species reacting	T(°C)	Slope [c]	Species reacting
(3)	4-NO_2		4′	25	0·96	0·998		C.A.		*d*	
(4)	4-NO_2	2-Me	4′	25	0·38	0·999	0·62	F.B	25	0·28	C.A
(5)	4′-NO_2		4	40	0·43	0·990	0·81 [e]	F.B	40	0·53	C.A
(6)	4′-NO_2	2-Me	4	25	0·45	0·987	0·71 [e]	F.B	25	0·30	C.A
(11)	4-NO_2	5-OMe	4′	50	1·04	0·992		C.A	25	0·22	C.A
(12)	4′-NO_2	5-OMe	4	40	0·85	0·988		C.A	40	0·36	C.A

[a] Moodie–Schofield plots. [b] Corrected for free base concentration. [c] d log k_2(obs)/dH_0 (92—98% H_2SO_4). [d] Because of high reactivity in high acidity region, it was not possible to construct the high rate profile. [e] The values utilise estimated values of *m*, see text.

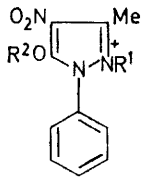
TABLE 7

Arrhenius parameters [a]

No.	Compound	H_2SO_4%	$\Delta H^\ddagger$ kcal mol^{-1}	$\Delta S^\ddagger$ cal mol^{-1} K^{-1}	$\Delta G^\ddagger_{25°}$ kcal mol^{-1}	log A
(4)	2,3-Dimethyl-4-nitro-1-phenyl-Δ^3-pyrazolin-5-one	84·1	15·8 11·0 [b]	−15·1 −17·1 [a]	20·3 15·9 [a]	10·0 9·5 [a]
		91·2	12·6	−24·3	19·9	7·9
(5)	3-Methyl-1-*p*-nitrophenyl-5-pyrazolone	96·2	10·9	−24·1	18·1	8·0
(6)	2,3-Dimethyl-1-*p*-nitrophenyl-Δ^3-pyrazolin-5-one	84·1	17·2 13·4 [b]	−17·0 −3·2 [a]	22·3 14·3 [a]	10·8 12·5 [a]
		91·2	8·9	−36·3	19·7	5·3

[a] Calculated using the equation $\Delta H^\ddagger/T - \Delta S^\ddagger = (10{\cdot}319)\ (4{\cdot}574) - (4{\cdot}574)\log k_2$(obs) where log k_2(obs) values refer to a constant % H_2SO_4. [b] Calculated using log k_2(fb) as defined by equation (2).

solvent and thus increase the charge density on the heterocyclic ring.



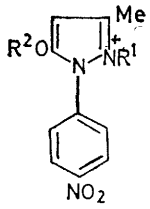
(15) $R^1 = R^2 = H$
(16) $R^1 = Me$, $R^2 = H$
(17) $R^1 = H$, $R^2 = Me$

As the acid concentration is reduced, the concentration of the neutral species increases, and a changeover in mechanism to nitration as the free base occurs for 4-nitroantipyrine (4), but not for the two other compounds [(3) and (11)]. The basicity of the methoxypyrazole (11) is (at pK_a — 1·59) but little higher than that of the corresponding pyrazolone (Table 3). We ascribe the changeover for (16) to an illustration of the selectivity relationship: for less reactive substrates, the rate of reaction is more susceptible to structural changes, in this case to rate decreases on protonation.

solvent relative to that in (18) also has a rate-decreasing effect.

The two compounds which can exist as pyrazolones [(5) and (6)] show nitration as the free-base species in the low acidity region: this indicates that (5) is being nitrated in the Δ^3-tautomeric form indicated. That (5) reacts faster than (6), reflects the steric hindrance in (6).

Partial rate factors (Table 8) were calculated for these compounds by the procedure described: [25] they will be



(18) $R^1 = R^2 = H$
(19) $R^1 = Me$, $R^2 = H$
(20) $R^1 = H$, $R^2 = Me$

discussed later with those for other heteroaromatic compounds, but the low partial rate factor for compound (12) together with the high selectivity to attack at the *para*-position is similar to that found in the 1-phenylpyrazole series.[25]

TABLE 8

Partial rate factors (p.r.f.) [a]

Compound	Ring substituents		Species	T(°C)	log $k_2(T)$	E_a	log k_2(25°)	P.r.f.	log k_2 25°(fb)	P.r.f. (fb)
(3)	4-NO_2		C.A	25	−0·35		−0·35	1·29 × 10^{-1}		
(4)	4-NO_2	2-Me	F.B	25	−3·35		−3·35		−1·16	1·98 × 10^{-2}
(5)	4′-NO_2		F.B	40	−1·44	25 [b]	−2·21		1·59 [c]	4·15
(6)	4′-NO_2	2-Me	F.B	25	−4·24		−4·24		−0·44 [c]	1·04 × 10^{-1}
(11)	4-NO_2	5-OMe	C.A	50	−3·42	11·6 [d]	−4·08	2·4 × 10^{-5}		
(12)	4′-NO_2	5-OMe	C.A	40	−5·14	11·6 [d]	−5·55	8·1 × 10^{-7}		

[a] At standard conditions [*i.e.* 25° and 75% H_2SO_4]. [b] Estimated value (*cf.* ref. 25). [c] Calculated using estimated pK_a values. [d] Assumed as a typical value for conjugate acid nitrations (*cf.* ref. 25).

Relative Nitration Rates at the 4-Position of the Pyrazole Ring.—Compounds (5), (6), and (12) form cations (18)—(20) respectively. In the high acidity region, it is evident that the rates vary in the order (18) > (19) ≫ (20). For these cations, we believe that positive charge dispersal over the phenyl ring from the pyrazolium ring is important. Such dispersal is easiest for (18) which enjoys the greatest conjugation between the two rings: in (19) and (20) reduction of hydrogen bonding with the

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[25] A. G. Burton, A. R. Katritzky, M. Konya, and H. O. Tarhan, following paper.