Heteroaromatic Reactivity. Part VII.[1] The Kinetics, Products, and Mechanism of Nitration of Some 1-Arylpyrazoles and 1-Phenylimidazole

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The nitration in sulphuric acid of some 1-arylpyrazoles, and of 1-phenylimidazole, to give substitution in the carbocyclic rings is shown to involve the cations of the bases. Methyl groups at N-2 or C-5 in the 1-arylpyrazoles reduce reactivity in nitration by steric hindrance to the coplanarity of the aryl and heterocyclic group. Nitration of 1-arylpyrazoles in acetic anhydride generally gives poor yields of mononitro-compounds substituted at C-4 of the pyrazole ring. However, 5-methyl-1-phenylpyrazole gives both 5-methyl-3- and 5-methyl-4-nitro-1-phenylpyrazole. The poor yields prevent a definite assignment of mechanism; some possibilities are briefly discussed.

It is well known that the orientation of mononitration of 1-phenylpyrazole depends on the reagent used; mixed acid gives 1-(*p*-nitrophenyl)pyrazole,[2,3] whilst a solution prepared from nitric acid and acetic anhydride gives 4-nitro-1-phenylpyrazole.[2,4] Nitronium tetrafluoroborate in sulpholan also causes 4-nitration.[5] Similar results have been obtained with a number of derivatives of 1-phenylpyrazole.[6]

It has been suggested that in the case of 1-phenylpyrazole,[4] and also of some of its analogues,[7] that the use of mixed acid leads to nitration of the conjugate acid of the base, whilst nitric acid in acetic anhydride nitrates the free base, the change in the reacting form of the substrate leading to the change of orientation. The result obtained with nitronium tetrafluoroborate was adduced to support this view.[5]

In this paper we report the application to the behaviour of some 1-arylpyrazoles of some of the criteria which have been developed to distinguish between free base and conjugate acid nitration.[8] Other 1-arylazoles have been less extensively studied than the pyrazoles. 1-Phenylimidazole gives 1-(*p*-nitrophenyl)imidazole

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[3] I. L. Finar and R. J. Hurlock, *J. Chem. Soc.*, 1957, 3024.
[4] M. A. Khan, B. M. Lynch, and Y.-Y. Hung, *Canad. J. Chem.*, 1963, **41**, 1540.
[5] B. M. Lynch and Y.-Y. Hung, *Canad. J. Chem.*, 1964, **42**, 1605.
[6] 'Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings,' ed. R. H. Wiley, Interscience Publishers, New York, 1967.
[7] D. Dal Monte Casoni, *Ann. Chim.* (*Italy*), 1958, **48II**, 783; *Gazzetta*, 1959, **89**, 1539.
[8] Other papers in this series, and also 'Nitration and Aromatic Reactivity,' J. G. Hoggert, R. B. Moodie, J. R. Penton, and K. Schofield, Cambridge University Press, 1971.

when nitrated in sulphuric acid,[9] and we have examined the kinetics of this reaction.

EXPERIMENTAL

Materials.—AnalaR sulphuric acid (*d* 1·84) and acetic anhydride were used. Nitric acid was purified by the method described in earlier papers.[10] Aqueous solutions of sulphuric acid were prepared by diluting the AnalaR acid with distilled water; the solutions were standardised by density measurements. 3-Methyl-1-phenylpyrazole was commercial material (Koch–Light; puriss), m.p. 35—36 °C (lit.,[11] 35·5—36·5 °C). The following, known compounds were prepared by standard methods: 1-phenylpyrazole, b.p. 90 °C at 0·5 mmHg, n_D^{25} 1·5950 (lit.,[3,4] 74 °C at 0·05 mmHg; n_D^{25} 1·5957); 5-methyl-1-phenylpyrazole, b.p. 142 °C at 20 mmHg (lit.,[6] 263·5 °C at 762 mmHg); 3,5-dimethyl-1-phenylpyrazole, b.p. 114—118 °C at 1·2 mmHg (lit.,[6] 273 °C at 754 mmHg), 1-(*o*-tolyl)pyrazole, b.p. 242 °C at 760 mmHg (lit.,[12] 240—242 °C at 760 mmHg); and 1-phenylimidazole, b.p. 125—130 °C at 5 mmHg, n_D^{23} 1·5980 (lit.,[13] 142 °C at 15 mmHg; n_D^{25} 1·6025).

[4-$^2H_1$]5-*Methyl-1-phenylpyrazole.*— 5-Methyl-1-phenylpyrazole was heated with deuterium oxide at 200 °C for 12 h and the process was then repeated. N.m.r. spectroscopy indicated 80% exchange at C-4. The mass spectrum showed a strong molecular ion at 159 m.u.

1-*Methyl-2-phenylpyrazolium Perchlorate.*— 1-Phenylpyrazole (1·58 g) and methyl iodide (10 cm^3) were heated in the dark at 100 °C for 6 h, more methyl iodide being added from time to time. Excess of methyl iodide was removed *in vacuo* and the residue in methanol was treated with silver perchlorate (2·3 g) in acetone (10 cm^3). Silver iodide was removed, solvent was evaporated from the filtrate, and the residue was dissolved in hot ethanol. Crystals separated and on recrystallisation from ethanol gave the *methoperchlorate* (1·1 g), m.p. 154—156 °C (Found: C, 46·4; H, 4·5; N, 11·1. $C_{10}H_{11}ClN_2O_4$ requires C, 46·4; H, 4·3; N, 10·8%), $\lambda_{max.}$ (85·06% H_2SO_4) 230 nm (log ε 3·77).

4-*Nitro*-1-(o-*tolyl*)*pyrazole.*—*o*-Tolylhydrazine hydrochloride (12·3 g), sodium nitromalonaldehyde (17 g), and ethanol (75 cm^3) were heated together under reflux for 2 h. The solvent was removed and the dark brown residue was digested with water (200 cm^3) and neutralised with sodium carbonate solution. Extraction with ether, and removal of the ether after drying ($MgSO_4$) gave a solid (9·1 g), m.p. 56—57 °C, which was passed in benzene over alumina. Removal of the benzene and recrystallisation from ethanol gave colourless needles of 4-*nitro*-1-(o-*tolyl*)*pyrazole*, m.p. 67—68 °C (Found: C, 58·9; H, 4·4; N, 20·7. $C_{10}H_9N_3O_2$ requires C, 59·1; H, 4·5; N, 20·7%).

1-(2,6-*Dimethylphenyl*)*pyrazole.*— 2,6-Dimethylphenylhydrazine hydrochloride (10·1 g), 1,1,3,3-tetramethoxypropane (10·2 g), and ethanol (100 cm^3) were heated under reflux for 2 h. Ethanol was removed, the brown oil was poured into water (200 cm^3), and the mixture was neutralised with sodium carbonate. Ether extraction, drying of the extract ($MgSO_4$), and removal of ether gave an oil (6·9 g). Distillation gave a pale yellow oil, b.p. 70 °C at 0·2 mmHg, which was dissolved in ether and treated with hydrogen chloride. The precipitate was crystallised from absolute ethanol giving chunky crystals of 1-(2,6-*dimethylphenyl*)*pyrazole hydrochloride*, m.p. 137—139 °C (Found: C, 63·3; H, 6·2; N, 13·6. $C_{11}H_{13}ClN_2$ requires C, 63·3; H, 6·3; N, 13·4%).

Kinetic Measurements.—Rate constants were evaluated from the changes in absorbance with time of the reacting solutions, measured in a Unicam SP 800 spectrophotometer fitted with a thermostatted cell holder (25·0 ± 0·1 °C), as described previously.[10,14]

^1H *N.m.r. Spectroscopy.*—Spectra were recorded at 60 MHz (Perkin-Elmer R10) or 100 MHz (JEOL MH100) for deuteriochloroform solutions. Some of the nitrations in acetic anhydride were studied by recording the n.m.r. spectra of the reacting solutions; under the latter conditions useful information could only be obtained over the range τ 0—7 because of the strong solvent signal.

Mass Spectroscopy.—The mass measurements were made on a Hitachi–Perkin-Elmer RMU-6 instrument.

Preparative Nitrations in Sulphuric Acid.—1-*Phenylpyrazole.* The base (0·578 g) in 82·1% sulphuric acid (30 cm^3) was treated with a solution of fuming nitric acid (2·5 g) in 82·1% sulphuric acid (25 cm^3) at room temperature. After 12 h the solution was poured onto ice and neutralised with solid sodium carbonate. 1-(*p*-Nitrophenyl)pyrazole (0·711 g, 93·7%), m.p. 175—176 °C (Found: C, 57·3; H, 3·5; N, 22·2. Calc. for $C_9H_7N_3O_2$: C, 57·1; H, 3·7; N, 22·2%), was precipitated. Finar and Hurlock [3] gave m.p. 169—170 °C. T.l.c. (toluene–alumina) gave a single spot, R_F = 0·64. 1-(*p*-Nitrophenyl)pyrazole prepared from *p*-nitrophenylhydrazine hydrochloride and 1,1,3,3-tetramethoxypropane behaved identically, $\lambda_{max.}$ (77·7% H_2SO_4) 278 nm (log ε 4·12), *m/e* 189, 173, 159, 143, 142, 131, 117, 116, 90, 89, and 76 m.u., metastable ions at 108·1 (= 143^2/189; loss of NO_2· from $M^{+\cdot}$), 94·12 (= 116^2/142), and 95·74 (= 117^2/143).

3-*Methyl*-1-*phenylpyrazole.* The base (0·4332 g) in 80·2% sulphuric acid (30 cm^3) was treated at room temperature with a solution of fuming nitric acid (2·5 g) in 80·2% sulphuric acid (20 cm^3). After 30 min the solution was worked up as described above. Recrystallisation of the precipitate from aqueous ethanol gave 3-methyl-1-(*p*-nitrophenyl)-pyrazole (0·5406 g, 96·7%), m.p. 167 °C (Found: C, 58·8; H, 4·3; N, 20·6. Calc. for $C_{10}H_9N_3O_2$: C, 59·1; H, 4·5; N, 20·7%). Finar and Hurlock [15] give m.p. 170 °C. $\lambda_{max.}$ (75·5% H_2SO_4) 290 and 218 nm (log ε_{290} 4·09), *m/e* 203, 202, 187, 173, 157, 156, 155, 145, 142, 130, 128, 117, 116, 104, 103, 90, 89, 77, 76, and 55; metastable ions at 172·2 (= 187^2/203; loss of O from $M^{+\cdot}$) and 121·4 (= 157^2/203; loss of NO_2· from $M^{+\cdot}$).

5-*Methyl*-1-*phenylpyrazole.* The nitration of the base (0·3308 g) was carried out in 82·1% sulphuric acid as described for other cases. After dilution and basification of the solution the product was isolated by ether extraction. Recrystallisation from aqueous ethanol gave 5-methyl-1-(*p*-nitrophenyl)pyrazole, (0·379 g; 98·1%), m.p. 79 °C (Found: C, 59·2; H, 4·6; N, 20·8. Calc. for $C_{10}H_9N_3O_2$: C, 59·1; H, 4·5; N, 20·7%) (lit.,[16] m.p. 80—81 °C, $\lambda_{max.}$ (80·2% H_2SO_4) 268 nm (log ε 3·91) (shoulder at 215 nm),

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[16] J. Elguero and R. Jacquier, *Bull. Soc. chim. France*, 1966, 2832.

m/e 203, 202, 201, 187, 173, 157, 156, 155, 145, 130, 129, 128, 118, 103, and 91; metastable ions at 120·5 (= $156^2/202$; loss of $NO_2^{\bullet}$ from $M^{+\bullet} - H^{\bullet}$), 107·6 (= $130^2/157$; loss of HCN from 157), and 81·6 (= $103^2/130$; loss of HCN from 130).

1-(o-*Tolyl*)*pyrazole*. The base (0·493 g) was nitrated for 4 h in 79·2% sulphuric acid. Recovery of the product by ether extraction gave 0·606 g (96·8%) of an oil, τ (60 MHz) 7·62 and 7·72 (2 × s, total 3H), 3·51 (t, 1H), and 1·80—2·60 (m, 5H). The ratio of the two signals from the methyl groups was approximately 8 : 1. Chromatography of the mixture (benzene–light petroleum on basic alumina) gave about 0·21 g of the pure, major nitration product and 0·37 g of unresolved mixture. The n.m.r. spectrum (60 MHz) of the pure fraction gave signals at τ 7·63 (s, 3H), 3·52 (unsymmetrical t, 1H), and a multiplet (5H) similar to that already described. The multiplet was resolved by recording the n.m.r. spectrum at 100 MHz. Two signals, τ 2·26 (d, 1H) and 2·30 (d, 1H), were assigned to the 5- and 3-protons respectively of the pyrazole ring. The remaining signals of the multiplet, assigned to the aromatic protons, resembled those given by 4-nitro-*o*-xylene.

1-(2,6-*Dimethylphenyl*)*pyrazole*. The base (0·173 g) dissolved in 79·2% sulphuric acid (10 cm^3) was treated with pure nitric acid (0·076 g) in 79·2% sulphuric acid (10 cm^3). After 30 min the solution was quenched in water and the crude product was obtained by ether extraction, as described above; a pale yellow solid was obtained (0·20 g, 92%). Recrystallisation from petroleum ether gave colourless plates of 1-(2,6-*dimethyl*-3-*nitrophenyl*)*pyrazole*, m.p. 89—91 °C (Found: C, 61·2; H, 5·2; N, 19·5. $C_{11}H_{11}N_3O_2$ requires C, 60·8; H, 5·1; N, 19·4%). The n.m.r. data are given in Table 1.

3,5-*Dimethyl*-1-*phenylpyrazole*. Nitration of the base (1·800 g) in 87·6% sulphuric acid (30 cm^3) with pure nitric acid (0·75 g) gave a mixture of mono- and di-nitration products. After 1 h, the reaction mixture was quenched in water and the precipitate [mainly 3,5-dimethyl-4-nitro-1-(*p*-nitrophenyl)pyrazole (0·27 g)] was filtered off. The aqueous layer was extracted with ether and the ether extracts, after drying ($MgSO_4$), were evaporated to give a yellow solid. Recrystallisation from aqueous ethanol gave fine pale yellow needles of 3,5-dimethyl-1-(*p*-nitrophenyl)-pyrazole (0·743 g, 33%), m.p. 101—103 °C (lit.,[6] 99·5—102 °C), $\lambda_{max.}$ (80·2% H_2SO_4) 278 nm (log ε 4·06). ^1H N.m.r. data are given in Table 1. Examination of the u.v. spectra of reacting solutions showed that under the kinetic conditions only mononitration was occurring; u.v. extinction curves calculated assuming complete conversion into 3,5-dimethyl-1-(*p*-nitrophenyl)pyrazole agreed with the observed ' infinity ' curves.

1-*Phenylimidazole*. The base (0·158 g) in 72·9% sulphuric acid (10 cm^3) was treated with nitric acid (6·3 g) in 72·9% sulphuric acid (5 cm^3). After 12 h the reaction solution was worked-up as usual. Ether extraction recovered 1-(*p*-nitrophenyl)imidazole (0·187 g, 96·2%), m.p. 198 °C. Recrystallisation from aqueous ethanol raised the m.p. to 208 °C (Found: C, 57·2; H, 3·9; N, 22·2. Calc. for $C_9H_7N_3O_2$: C, 57·1; H, 3·7; N, 22·2%) (lit.,[9] 204—205 °C). (Use of 80·4% sulphuric acid in the nitration gave 88·3% of product.) T.l.c. (2 : 1 benzene–chloroform on alumina) gave a single spot, R_F = 0·7, τ (60 MHz) 1·90 (s, 1H), 1·4, 1·6, 2·2, and 2·4 (AB q, 4H), 2·5 (s, 1H), and 2·6 (s, 1H). *m/e* 189, 173, 162, 159, 143, 142, 132, 116, 104, 89, 76, 63, and 50; isotope ratio calculations confirm the molecular ion to be $C_9H_7N_3O_2$; metastable ions at 138·9 (= $162^2/189$, $M^{+\bullet} - HCN$), 108·1 (= $143^2/189$, $M^{+\bullet} - NO_2^{\bullet}$), and 94·12 (= $116^2/143$, 143 − HCN), $\lambda_{max.}$ (77·7% H_2SO_4) 272 nm (log ε 3·99). The spectrum changed with time, log ε at 280 nm changing from 0·83 to 0·75 in 24 h and then rising to 0·77 after 180 h, with a shoulder forming at 325 nm.

Preparative Nitrations in Acetic Anhydride.—1-*Phenylpyrazole*. A solution of pure nitric acid (0·99 g) in acetic anhydride (10 cm^3) was prepared and allowed to stand at room temperature for about 15 min before being cooled to 0 °C. This solution was then added to one of the base (0·426 g) in acetic anhydride (5 cm^3), the mixture being maintained at 0 °C. After 2 h, the mixture was poured into water and the aqueous solution was extracted with ether. After washing (sodium bicarbonate solution followed by water), and drying ($MgSO_4$), the ether was evaporated to give a yellow solid. Chromatography of the product (benzene–light petroleum on basic alumina), followed by recrystallisation from benzene–light petroleum gave needles of 4-nitro-1-phenylpyrazole (0·307 g, 55%), m.p. 125—127 °C (lit.,[4] 125—127 °C). ^1H N.m.r. data are given in Table 1.

3-*Methyl*-1-*phenylpyrazole*. The base (0·491 g) was nitrated using the above procedure, the reacting mixture being left for 1 h before quenching. The product, obtained by ether extraction, on recrystallisation from benzene–light petroleum gave needles of 3-methyl-4-nitro-1-phenylpyrazole (0·512 g, 80%), m.p. 110—111 °C (lit.,[5] 110 °C). ^1H N.m.r. data are given in Table 1.

5-*Methyl*-1-*phenylpyrazole*. Nitration of the base (0·458 g) by the above procedure (reaction time 3 h), gave an orange oil, which on chromatography (benzene on basic alumina) gave a pale yellow solid (0·328 g, 56%). ^1H N.m.r. spectroscopy showed this to be a mixture of the 3- (75%) and 4-nitro-isomers (25%). Repeated recrystallisation from benzene–light petroleum resulted in a pure sample of 5-methyl-3-nitro-1-phenylpyrazole, m.p. 97—98 °C (lit.,[6] 96 °C). ^1H N.m.r. data are given in Table 1.

3,5-*Dimethyl*-1-*phenylpyrazole*.—The base (0·629 g) was nitrated by the usual method (see above), the reaction time being 2·5 h. Chromatography of the crude product (benzene on basic alumina) followed by recrystallisation from petroleum ether, gave plates of 3,5-dimethyl-4-nitro-1-phenylpyrazole (0·330 g, 42%), m.p. 103—105 °C (lit.,[6] 103—104 °C). ^1H N.m.r. data are given in Table 1.

1-(o-*Tolyl*)*pyrazole*. The nitration mixture was prepared as described for 1-phenylpyrazole, but it was allowed to stand at room temperature for 22 h (0·56 g of the base was used). Light brown crystals were obtained by the usual work-up, which after chromatography (benzene on basic alumina) and recrystallisation from ethanol gave needles of 4-nitro-1-(*o*-tolyl)pyrazole (0·47 g, 65%), m.p. 67—68 °C. The i.r. and n.m.r. spectra were identical with those of an authentic sample of 4-nitro-1-(*o*-tolyl)pyrazole prepared by ring synthesis (*vide supra*).

1-(2,6-*Dimethylphenyl*)*pyrazole*. The base (0·55 g) was nitrated by the method described for 1-(*o*-tolyl)pyrazole, the reacting solution being allowed to stand for 40 h. A brown oil was isolated by the usual procedure and this gave, after chromatography (benzene on basic alumina), a pale yellow oil (0·48 g). The n.m.r. spectrum indicated that the oil was a mixture of starting material and 4-nitro-(2,6-dimethylphenyl)pyrazole in the ratio 3 : 1.

The preparative nitration was repeated with a threefold increase in the amount of nitric acid (2·9 g). A light brown

solid was isolated, which gave colourless plates after being recrystallised from ethanol, m.p. 141—142 °C. The n.m.r. spectrum (Table 1) was consistent with the compound being 4-nitro-1-(2,6-dimethyl-3-nitrophenyl)pyrazole.

RESULTS

^{1}H *N.m.r. Spectra.*—Previous work has shown that substituted pyrazoles can be conveniently characterised by their ^{1}H n.m.r. spectra,[5,17-19] and we have relied heavily on this criterion of structure. Our own data for the compounds studied in this work are presented in Table 1, and where comparison is possible with published results the agreement is good. In all cases the signals showed the expected multiplicities and gave the correct integration. The signal due to H-4 occurs at higher field than those due to the other protons and is easily identified. The protons of the 1-aryl substituent give rise to either a complex multiplet or a fairly well defined singlet. The latter case obtains if there is a substituent either at the 5-position of the pyrazole ring or at the 2-position of the phenyl ring. H-3 and H-5 give signals at low field and the signal due to H-5 is usually at lower field than that due to H-3;[5] the assignments in Table 1 for new data were made on the basis of this supposition.

TABLE 1

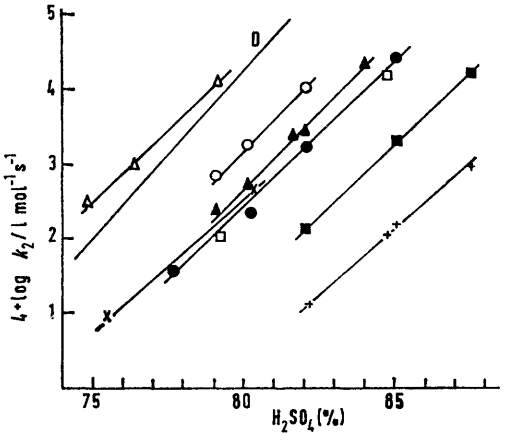
^{1}H N.m.r. parameters of substituted pyrazoles in deuteriochloroform [a,b]

Pyrazole	Chemical shifts (τ) C-3		C-4		C-5		Phenyl [c]		J_{AB}/Hz	Ref.
1-Phenyl		(2·26)	3·65	(3·55)		(2·06)	2·10—3·00	(2·40—2·80)		17
1-(*p*-Nitrophenyl)	1·97		3·45		1·90		1·67, 2·12		9·0	
4-Nitro-1-phenyl	1·72				1·34		2·14—2·60			
3-Methyl-1-phenyl	7·63	(7·65)	3·80	(3·77)	2·22	(2·22)	2·30—2·90	(2·30—2·80)		17
3-Methyl-1-(*p*-nitrophenyl)	7·62	(7·60)	3·65	(3·66)	2·06	(2·09)	1·68, 2·18	(1·71, 2·20)	9·0	18
3-Methyl-4-nitro-1-phenyl	7·38	(7·40)			1·40	(1·40)	2·20—2·70	(2·67—2·84)		5
5-Methyl-1-phenyl	2·46	(2·44)	3·85	(3·81)	7·71	(7·66)	2·60	(2·57)		17
5-Methyl-1-(*p*-nitrophenyl)	2·30	(2·36)	3·68	(3·70)	7·51	(7·52)	1·58, 2·24	(1·64, 2·30)	8·6	18
5-Methyl-3-nitro-1-phenyl			3·20		7·64		2·52			
5-Methyl-4-nitro-1-phenyl		(1·76)				(7·36)		(2·50)		19
3,5-Dimethyl-1-phenyl	7·74	(7·73)	4·05	(3·99)	7·74	(7·70)	2·63	(2·61)		17
3,5-Dimethyl-1-(*p*-nitrophenyl)	7·73	(7·70)	3·93	(3·91)	7·60	(7·56)	1·68, 2·33	(1·69, 2·33)	9·1	18
3,5-Dimethyl-4-nitro-1-phenyl	7·41				7·38		2·49			
1-(*o*-Tolyl)	2·40		3·56		2·27		2·69; 7·78			
4-Nitro-1-(*o*-tolyl)	1·76				1·66		2·64; 7·76			
1-(2,6-Dimethylphenyl)	2·55		3·55		2·27		2·83; 8·00			
1-(2,6-Dimethyl-3-nitrophenyl)	2·50		3·50		2·25		2·10, 2·74; 7·90; 7·94		8·7	
4-Nitro-1-(2,6-dimethylphenyl)	1·80				1·71		2·76; 7·94			
4-Nitro-1-(2,6-dimethyl-3-nitrophenyl)	1·70				1·62		1·95, 2·61		8·7	

[a] Chemical shifts quoted refer to the positions of the centres of the relevant multiplets. Chemical shifts of 3- and 5-protons were assigned assuming $\tau_3 > \tau_5$. [b] References are to published data given in parentheses. [c] Figures given refer to either range of τ covered by multiplet, or the centres of the doublets of the AB (or A_2B_2) quartet.

Nitrations in Sulphuric Acid.—Good first-order kinetics were observed with all the pyrazoles studied. The second-order rate constants (Table 2) were derived from the first-order rate constants and the known concentrations of nitric acid. For some of the slower runs (the cases are indicated in Table 2) an initial rates technique was used to calculate the rate constants. The rate profiles for the various substituted pyrazoles are shown in the Figure; the slopes all fall in the range 0·36—0·39 and this indicates that the majority species are being nitrated.[8] In all cases the u.v. spectrum of the reaction solution at the end of the nitration was that expected for mononitration.

Preparative nitrations gave almost quantitative yields (92—98%) of mononitro-products, in which substitution was in the phenyl ring. The 1-phenyl compounds were nitrated at the *p*-position whilst 1-(2,6-dimethylphenyl)pyrazole was nitrated at the 3-position. Two mononitration products were obtained from 1-(*o*-tolyl)pyrazole in the ratio *ca.* 8 : 1, as indicated by integration of the signals due to the methyl protons in the n.m.r. spectrum. The spectrum also showed the major nitration product to be either 1-(2-methyl-4-nitrophenyl)- or 1-(2-methyl-5-nitrophenyl)-pyrazole, but the minor component was not characterised.



Rate profiles for nitration in sulphuric acid at 25 °C: △, 1-(2,6-dimethylphenyl)pyrazole; ○, 3-methyl-1-phenylpyrazole; ▲, 1-(*o*-tolyl)pyrazole; ×, 1-phenylimidazole; ●, 1-phenylpyrazole; □, 3,5-dimethyl-1-phenylpyrazole; ■, 5-methyl-1-phenylpyrazole; +, 1-phenylpyrazole methoperchlorate; D, *p*-dichlorobenzene, data from R. G. Coombes, D. H. G. Crout, J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1970, 347.

The instability of 1-(*p*-nitrophenyl)imidazole in sulphuric acid (see Experimental section) made it necessary to use

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[19] I. L. Finar and E. F. Mooney, *Spectrochimica Acta*, 1964, **20**, 1269.

the initial rate method, although good rate constants were obtained regardless of whether the observed infinity spectrum or one calculated from the spectrum of 1-(*p*-nitrophenyl)imidazole in sulphuric acid was used. The course of decomposition of 1-(*p*-nitrophenyl)imidazole in sulphuric acid was not examined.

Nitrations in Acetic Anhydride.—These did not show simple kinetic behaviour. Although the first order plots for some of the compounds, *e.g.* 1-phenylpyrazole, 3- and 5-methyl-1-phenylpyrazole were fairly linear, those for 3,5-dimethyl-1-phenylpyrazole showed distinct curvature. Furthermore, in all cases the u.v. spectrum of the reaction solution after complete nitration showed a higher absorbance than that calculated on the basis of a quantitative conversion into the expected nitration product. With 5-methyl-1-phenylpyrazole, for example, the observed infinity spectrum showed an absorbance over twice as great as that calculated. This behaviour is probably connected with the fact (*vide infra*) that the yields of nitration products from preparative nitrations in acetic anhydride are invariably low. The anomalous kinetic behaviour of these compounds is also apparent from the slopes of their rate profiles, given after the name of the compound; 1-phenylpyrazole (*ca.* 3), 3-methyl-1-phenylpyrazole (2·4), 5-methyl-1-phenylpyrazole (1·4), and 3,5-dimethyl-1-phenylpyrazole (1·2). Under the conditions of nitration used, a slope of 3 would have been expected for each compound.[10,20]

TABLE 2

Second-order rate constants for nitrations in sulphuric acid at 25 °C [a]

H_2SO_4 (%)	$10^2[HNO_3]$/mol l^{-1}	k_2/l mol^{-1} s^{-1}
1-Phenylpyrazole		
77·7	2·60	$3·86 \times 10^{-3}$
80·2	1·66	$2·33 \times 10^{-2}$
82·1	2·54	$1·71 \times 10^{-1}$
85·1	1·69	2·50
3-Methyl-1-phenylpyrazole		
79·2	1·51	$6·37 \times 10^{-2}$
80·2	0·972	$1·68 \times 10^{-1}$
82·1	0·981	1·25
5-Methyl-1-phenylpyrazole		
82·1	1·91	$1·30 \times 10^{-2}$
85·1	1·08	$1·87 \times 10^{-1}$
87·6	1·70	1·54
3,5-Dimethyl-1-phenylpyrazole		
79·2	36·3	$1·09 \times 10^{-2}$
80·2	3·90	$2·36 \times 10^{-2}$
84·8	0·219	1·54
1-(*o*-Tolyl)pyrazole		
79·2	1·61	$2·18 \times 10^{-2}$
80·2	1·25	$4·78 \times 10^{-2}$
81·7	3·19	$2·16 \times 10^{-1}$
82·1	1·22	$2·45 \times 10^{-1}$
84·1	0·345	2·0
1-(2,6-Dimethylphenyl)pyrazole		
74·9	1·52	$2·78 \times 10^{-2}$
76·4	1·61	$9·35 \times 10^{-2}$
79·2	0·310	1·17
1-Phenylpyrazole methoperchlorate		
82·2	1·23	$1·31 \times 10^{-3}$ [b]
84·8	1·33	$1·06 \times 10^{-2}$ [b]
85·1	1·19	$1·52 \times 10^{-2}$ [b]
87·6	1·40	$8·86 \times 10^{-2}$
1-Phenylimidazole		
68·6	2·55	$3·29 \times 10^{-6}$ [b]
72·9	3·66	$6·13 \times 10^{-5}$ [b]
75·5	2·44	$9·15 \times 10^{-4}$ [b]
77·7	2·88	$4·11 \times 10^{-3}$
80·4	3·61	$4·30 \times 10^{-2}$

[a] [Aromatic] *ca.* 10^{-3}—10^{-5} mol l^{-1}. [b] Initial rates.

The preparative nitrations in acetic anhydride were characterised by the formation of tarry impurities, and yields of mono-nitro-products were generally low (40—75%). The pure compounds isolated all carried their nitro-groups in the pyrazole ring, and since they were stable in the nitrating media the poor yields and the formation of tars were not caused by decomposition of the mononitro-compounds. Earlier preparative nitrations were sometimes carried out at 25 °C, and yields were low, being improved by keeping the solutions at 0 °C.

1-(*o*-Tolyl)pyrazole and 1-(2,6-dimethylphenyl)pyrazole were much less reactive than the other 1-phenyl substituted pyrazoles. Whereas for the last mentioned compounds nitration was effected within 2 h under the conditions used, 1-(*o*-tolyl)pyrazole required 24 h at 25 °C for complete reaction, and 1-(2,6-dimethylphenyl)pyrazole was only partially nitrated after 40 h at 25 °C. Use of a higher concentration of nitric acid with the last mentioned compound led to dinitration; 4-nitro-1-(2,6-dimethyl-3-nitrophenyl)pyrazole was obtained.

The product of nitration of 5-methyl-1-phenylpyrazole was found to be mainly 5-methyl-3-nitro-1-phenylpyrazole (75% of the isolated products), together with a smaller amount of the 4-nitro-isomer (25%). Although the assignment of structures to the products is fairly certain from their n.m.r. spectra, the occurrence of 3-nitration was confirmed by nitrating [4-$^2H_1$]5-methyl-1-phenylpyrazole (80 atoms % deuterium at C-4). The n.m.r. spectrum of the nitration product again indicated a mixture of 3- and 4-nitro-isomers, with the peak assigned to H-4 of the 3-nitro-isomer showing the expected reduction in intensity because of the partial deuteriation at that position. With the other substrates, the only isolable products were the 4-nitro-compounds.

1-Phenylimidazole exhibited yet another type of behaviour. The u.v. spectrum of a solution of 1-phenylimidazole in acetic anhydride containing nitric acid showed a decrease in absorbance with time; formation of nitration product would lead to an increase in absorbance. The reaction was followed by n.m.r. spectroscopy; apart from an initial broadening and a small downfield shift of the peaks, the spectrum did not show any further change with time, at least during 20 h. On quenching the reaction solution in water and extracting with ether, 1-phenylimidazole was isolated. 1-Phenylimidazole nitrate, prepared separately, was found to be soluble in acetic anhydride giving a n.m.r. spectrum similar to that obtained above. Very similar observations were made with quinoline; the u.v. spectrum of a reaction solution in acetic anhydride showed a decrease with time, and quinoline nitrate was precipitated when nitric acid was added to a solution of quinoline in acetic anhydride contained in a n.m.r. tube.

DISCUSSION

Our results for nitration in sulphuric acid show that all the 1-arylpyrazoles which we have examined, and also 1-phenylimidazole react as the majority species

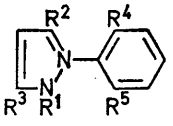
[20] S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1971, 2454.

present, and these must be the cations. Thus, nitration occurs in the 1-aryl groups because the heterocyclic nuclei are deactivated by protonation.

The remarkable feature of the results is the degree of de-activation which the protonated pyrazole nucleus imposes on the phenyl ring, along with almost quantitative *para*-orientation. In Table 3 we list the relative

TABLE 3

Relative rates of nitration in sulphuric acid at 25 °C



R^1	R^2	R^3	R^4	R^5	Relative rate [a]	f_p
H	H	H	Me	Me	$1{\cdot}2 \times 10^{-3}$	
H	H	Me	H	H	$4{\cdot}7 \times 10^{-5}$	28×10^{-5}
H	H	H	Me	H	$1{\cdot}2 \times 10^{-5}$	
H	H	H	H	H	$5{\cdot}9 \times 10^{-6}$	35×10^{-6}
H	Me	Me	H	H		
H	Me	H	H	H	$3{\cdot}5 \times 10^{-7}$	21×10^{-7}
Me	H	H	H	H	$2{\cdot}4 \times 10^{-8}$	14×10^{-8}
1-Phenylimidazolium					$1{\cdot}9 \times 10^{-5}$	11×10^{-5}
2-Phenylpyridinium					$8{\cdot}6 \times 10^{-5}$ [b]	25×10^{-5} [c]
4-Phenylpyridinium [d]					$2{\cdot}1 \times 10^{-4}$	6×10^{-4}
2-Nitrobiphenyl [e]					0·29	
4-Nitrobiphenyl [e]					0·49	

[a] Average value from the whole length of overlap of the rate profile of each compound with that of *p*-dichlorobenzene (Figure), related to the rate for benzene as unity by the factor $5{\cdot}9 \times 10^{-4}$ for the relative rate of nitration of *p*-dichlorobenzene [R. G. Coombes, D. H. G. Grout, J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1970, 347]. [b] Obtained using the rate data of Katritzky and Kingsland, *J. Chem. Soc.* (*B*), 1968, 862, and the comparison with *p*-dichlorobenzene. From a different basis of calculation Katritzky and Kingsland obtained the value $4{\cdot}9 \times 10^{-5}$. [c] From our value for the relative rate and the mean value for the proportion of *p*-substitutions reported by Katritzky and Kingsland. [d] Ref. 21. [e] R. G. Coombes and L. W. Russell, *J. Chem. Soc.* (*B*), 1971, 2443.

rates of nitration of the compounds studied, together with results for other compounds taken from the literature, and where appropriate, approximate values of the partial rate factors, f_p, for the *para*-position of the *N*-phenyl group calculated on the assumption that in the cases of the phenylazoles *para*-nitration occurs exclusively.

The results in Table 3 show the following sequence of abilities to deactivate the phenyl group: 2-methyl-1*H*-pyrazolium > 5-methyl-1*H*-pyrazolium > 3,5-dimethyl-1*H*-pyrazolium ≈ 1*H*-pyrazolium > 3-methyl-1*H*-pyrazolium ≈ pyridinium-2-yl ≈ pyridinium-4-yl ≫ 2- and 4-nitrophenyl. The values of f_p recorded for the 1-phenylpyrazoles (10^{-4}—10^{-7}) are amongst the smallest known, being not much larger than those (*ca.* 10^{-8}) associated with such substituents as NO_2 and $\overset{+}{N}Me_3$.[8] However, nitrobenzene and trimethylphenylammonium ion are, of course, nitrated chiefly at the *meta*-positions.

For 2- and 4-phenylpyridinium ions the ratio of *para* to (*ortho* + *meta*) nitration in the phenyl rings is not much different from unity, the amount of *meta*-substitution outweighing the amount of *ortho*-substitution in each case. For 1-phenyl-, and 3- and 5-methyl-1-phenylpyrazolium the ratio of *para* to (*ortho* + *meta*) substitution is *ca.* 20 : 1, and possibly considerably larger in the last two cases. (The orientation of nitration of 2-methyl-1-phenylpyrazolium was not determined, but there is no reason to doubt that it follows the same pattern.) In terms of the kind of discussions given [21] for the phenylpyridinium ions the increased difference between *para*- and *meta*-positions in the 1-phenylazoles could arise from a more effective combined field and inductive effect originating in the azolium rings, or from more effective conjugative release from the latter, or from both these causes.

In applying to the case of 1-phenylpyrazole being nitrated in sulphuric acid the criterion of comparison with the corresponding quaternary cation,[8] 2-phenyl-1-methylpyrazolium, we observed the marked fall in reactivity (>10^2, Table 3) produced by quaternisation. The obvious conclusion that steric hindrance by the methyl group of the coplanarity of the phenyl and pyrazole rings was responsible for this effect was borne out by the similar behaviour of 5-methyl-1-phenylpyrazolium. In contrast, the methyl group in 3-methyl-1-phenylpyrazolium exerts the more usual weakly activating effect, whilst in 3,5-dimethyl-1-phenylpyrazolium the effects of the methyl groups effectively cancel each other. The very considerable effect of introducing steric hindrance to coplanarity without otherwise altering the geometry of the molecule points to the reality of conjugative electron release from the pyrazolium nucleus.

As already mentioned, kinetic studies of the reactions occurring in acetic anhydride were rendered nugatory by their failure to produce quantitative mononitration. This aspect of these reactions has not hitherto been sufficiently remarked, and it, combined with the surprising observation of the formation of 5-methyl-3- as well as 5-methyl-4-nitro-1-phenylpyrazole from 5-methyl-1-phenylpyrazole suggests the need for caution in ascribing nitration at C-4 to a simple free base reaction on the evidence available.

Electrophilic substitutions into pyrazoles lacking *N*-aryl groups generally proceed at C-4.[6,22] This is true for nitration except in two circumstances; *N*-unsubstituted pyrazoles, whether substituted at C-4 or not, when nitrated in the presence of acetic anhydride give *N*-nitropyrazoles,[23,24] and some 1,4-disubstituted pyrazoles nitrated in acetic anhydride,[25] or with nitric acid or mixed acid [26] give 3-nitro- or 3,5-dinitro-pyrazoles. Acid-catalysed rearrangement of *N*-nitropyrazoles gives 4-nitropyrazoles,[23] whilst thermal rearrangement gives

[21] F. de Sarlo and J. H. Ridd, *J. Chem. Soc.* (*B*), 1971, 712.
[22] J. H. Ridd in 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, vol. I, 1963.
[23] R. Hüttel and F. Büchele, *Chem. Ber.*, 1955, **88**, 1586.
[24] J. W. A. M. Janssen and C. L. Habraken, *J. Org. Chem.*, 1971, **36**, 3081.
[25] C. L. Habraken, P. Cohen-Fernandes, S. Balian, and K. C. Van Erk, *Tetrahedron Letters*, 1970, 479.
[26] M. D. Coburn, *J. Heterocyclic Chem.*, 1971, **8**, 153.

3-nitropyrazoles and sometimes 4-nitropyrazoles.[24] The nitration of 5-methyl-1-phenylpyrazole seems to be the first one to be met in which a compound unsubstituted at C-4 reacts at C-3 as well as at C-4. Clearly the possibility exists that from 5-methyl-1-phenylpyrazole either one or both the identified products is produced by initial *N*-nitration.

If this were the case the intermediate product would be a quaternary salt (as it would be in related cases [26]), and either it or the more usual kind of Wheland intermediate would be susceptible to nucleophilic attack. Solutions prepared from nitric acid and acetic anhydride can certainly effect such attack,[27] so that it is perhaps not surprising that from the 1-arylpyrazoles yields of mononitro-compounds are low. These possibilities remain speculative without identification of the other products of reaction.

A general comment on one aspect of this work is conveniently made here. We have endeavoured recently [20] to develop a criterion for distinguishing between the nitration of a base and its cation additional to those earlier established; [8] the method is to compare the behaviour of a base on nitration in acetic anhydride with its behaviour on nitration in sulphuric acid. Applied to weak bases such as acetanilide ($pK_a \approx -1{\cdot}5$) the method works well. Our present results show that it fails with stronger bases such as quinoline ($pK_a = 4{\cdot}9$) and 1-phenylimidazole (pK_a probably *ca.* 6) which form salts in solutions prepared from nitric acid and acetic anhydride as well as in sulphuric acid. It also suggests that application of the method to some relatively weak bases may be vitiated by side reactions, perhaps involving nucleophilic attack on the substrate.

[2/575 *Received*, 13*th March*, 1972]

[27] D. J. Blackstock, M. P. Hartshorn, A. J. Lewis, K. E. Richards, J. Vaughan, and G. J. Wright, *J. Chem. Soc.* (*B*), 1971, 1212.