# The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XLVII.[1] Nitration of Phenylisoxazoles

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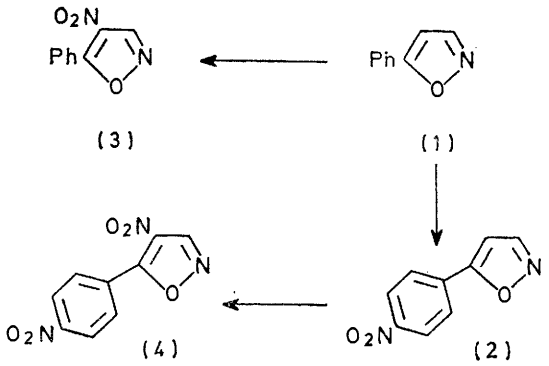
3-Methyl-5-phenylisoxazole undergoes nitration as the conjugate acid at the *para*-position of the phenyl group. 5-Methyl-3-phenylisoxazole undergoes nitration as the conjugate acid at the *meta*-position and also as the free base at the *para*-position of the phenyl group. Standard rates for nitration at 25 °C and $H_0$ −6.6 are calculated and the influence of the charged and neutral isoxazolyl substituents is discussed.

WHEREAS alkylisoxazoles undergo nitration at the 4-position of the heterocyclic ring, phenylisoxazoles are frequently substituted in the benzene ring. The precise orientation of such nitrations has been a matter of some controversy: Kochetkov and Khomutova [2] reported that 5-phenylisoxazole (1) with $H_2SO_4$–$HNO_3$ yields both 5-*p*-nitrophenyl- (2) and 4-nitro-5-phenyl-isoxazole (3), but Lynch and Shiu claim [3] that (2) is the sole mononitro-product and that is further nitrated to (4). 3,5-Diphenylisoxazole is reported [4] to yield the *para,para'* dinitro-derivative. 3-Phenylisoxazole was first [4] stated to yield the *para*-nitro-derivative, but reinvestigation [5a] indicated that a mixture of 3-*meta*- and 3-*para*-nitrophenyl derivatives was formed with $H_2SO_4$–$HNO_3$ but the 4-nitro-compound with $HNO_3$–$Ac_2O$. Recently the nitration of 3,5-diphenylisoxazole has been reinvestigated [5b] and found to give the 5-*p*-nitrophenyl and the 3-*m*-nitrophenyl-5-*p*-nitrophenyl analogues in mixed acid but the 4-nitro-derivative in acetic anhydride.

Following our work on the nitration of 3,5-dimethylisoxazole,[6] we have now investigated preparatively and kinetically the nitration of 3-methyl-5-phenylisoxazole (5), 5-methyl-3-phenylisoxazole (6), and the corresponding *N*-methyl cations (8) and (10) which serve as models for the protonated species (7) and (9), respectively. The methylphenylisoxazoles (5) and (6) were prepared by standard methods; the methoperchlorates (8), (12), (10), and (14) were made *via* the corresponding tosylates or trifluoromethanesulphonates.

The nitration of 3-methyl-5-phenylisoxazole (5) in $H_2SO_4$–$HNO_3$ was previously reported [7] as yielding the 5-*p*-nitrophenyl analogue (15), and we confirmed this




by n.m.r. spectroscopy (Table 1). However, in our hands, nitration in $Ac_2O$–$HNO_3$ gave the 4-nitro-5-*p*-nitrophenyl derivative (16) as the only product isolated, in poor yield.

We found that the nitration of 5-methyl-3-phenylisoxazole (6) gives both the corresponding 3-*p*-nitrophenyl (17) and 3-*m*-nitrophenyl derivatives (18) in mixed acid but the 4-nitro-3-*p*-nitro-compound (19) in

[1] Part XLVI, S. Clementi, A. R. Katritzky, and H. O. Tarhan, *Tetrahedron Letters*, 1975, 1395.
[2] N. K. Kochetkov and E. D. Khomutova, *Zhur. obshchei Khim.*, 1958, **28**, 359 (*Chem. Abs.*, 1958, **52**, 13,710*b*).
[3] B. M. Lynch and L. Shiu, *Canad. J. Chem.*, 1965, **43**, 2117.
[4] C. Musante, *Farmaco, Ed. sci. e tec.* (*Pavia*), 1951, **6**, 32 (*Chem. Abs.*, 1951, **45**, 5879*f*).
[5] [a] M. R. Langella and P. V. Finzi, *Chimica e Industria*, 1965, **47**, 996 (*Chem. Abs.*, 1965, **63**, 16,325a); [b] S. D. Sokolov, T. N. Yegorova and I. M. Yudintseva, *Khin. Geterotsikl, Soedinenii*, 1974, 597.
[6] A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2365.
[7] C. Musante, *Gazzetta.*, 1942, **72**, 537.

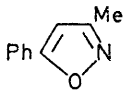
TABLE 1

Proton n.m.r. chemical shifts ($\tau$ values [a]) and coupling constants (Hz) of substituted isoxazoles and isoxazolium salts [b]

| | Isoxazole ring position | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | | | 4 | 5 | | |
| Compd. | | | | $J$ [c] | | | | $J$ [c] |
| (5) [d] | | Me | 7.69 | | H 3.63 | Ph | 2.05—2.07 | |
| (6) [d] | | Ph | 2.10—2.70 | | H 3.77 | Me | 7.61 | |
| (8) [e] | Me 5.74 | Me | 7.31 | | H 2.89 | Ph | 1.95—2.41 | |
| (10) [e] | Me 5.67 | Ph | 2.26 | | H 3.04 | Me | 7.28 | |
| (12) [e] | Me 5.59 | Me | 7.18 | | H 2.61 | $p$-$NO_2$·$C_6H_4$ | 1.38, 1.78 | 9 |
| (14) [e] | Me 5.60 | $m$-$NO_2$·$C_6H_4$ | 1.12—2.27 | | H 2.89 | Me | 7.18 | |
| (15) [d] | | Me | 7.58 | | H 3.41 | $p$-$NO_2$·$C_6H_4$ | 1.63, 2.03 | 9 |
| (16) [d] | | Me | 7.39 | | ($NO_2$) | $p$-$NO_2$·$C_6H_4$ | 1.58, 1.86 | 9 |
| (17) [d] | | $p$-$NO_2$·$C_6H_4$ | 1.71, 2.04 | 9 | H 3.64 | Me | 7.50 | |
| (18) [d] | | $m$-$NO_2$·$C_6H_4$ | 1.30—2.50 | | H 3.61 | Me | 7.50 | |
| (19) [d] | | $p$-$NO_2$·$C_6H_4$ | 1.59, 2.12 | 9 | ($NO_2$) | Me | 7.04 | |

[a] Relative to internal $Me_4Si$ for solutions in $CDCl_3$; for $D_2SO_4$ to tetramethylammonium sulphate ($\tau$ 6.81). [b] As perchlorate salts. [c] Coupling constants (Hz) for $p$-nitrophenyl substituents. [d] $CDCl_3$ as solvent. [e] $D_2SO_4$ as solvent.

$Ac_2O$–$HNO_3$. The orientations of all the nitrations were proved by the n.m.r. spectra (Table 1); the



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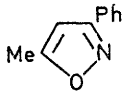
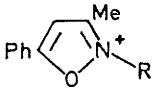
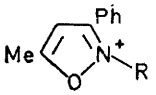


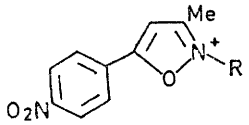
(6)



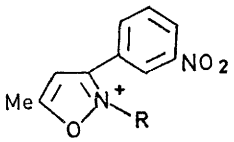
(7) R = H
(8) R = Me



(9) R = H
(10) R = Me

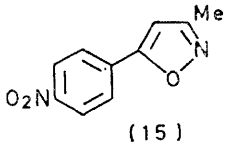


(11) R = H
(12) R = Me



(13) R = H
(14) R = Me

isoxazole 4-proton singlet signal at $\tau$ 3.4—3.8 (*cf.* refs. 8 and 9) and the coupling of the $A_2B_2$ pattern for the $p$-nitro-compounds was especially characteristic. In



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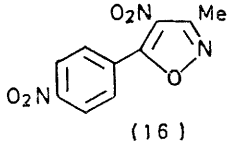
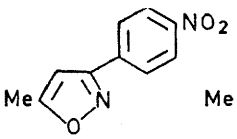


(16)

the 5-phenyl series spectra of the crude nitration product (91%) showed that the *para*-isomer predominated by at least 80% (by n.m.r.): the isolated yield of pure *para*-isomer was 58%.

[8] S. D. Sokolov, I. M. Yudintseva, and P. V. Petrovskii, *Zhur. org. Khim.*, 1970, **6**, 2584 (*Chem. Abs.*, 1971, **74**, 69,971n).

However in the 3-phenyl series, the proportions of the *meta*- (18) and *para*- (17) isomers depended on the acidity (Table 2).



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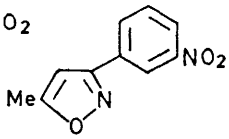
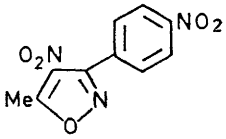


(18)



(19)

TABLE 2

Isomer ratios of the product composition from the nitration of 5-methyl-3-phenylisoxazole [a]

| % $H_2SO_4$ (w/w) | Time (h) | $T$/°C | % Yield (crude) | % $m$-Nitro | % $p$-Nitro |
|---|---|---|---|---|---|
| 70.0 | 120 | 100 | 26 | 5 | 95 |
| 73.5 | 72 | 100 | 48 | 15 | 85 |
| 75.5 | 72 | 60 | 70 | 23 | 77 |
| 77.9 | 24 | 80 | 72 | 28 | 72 |
| 81.5 | 12 | 40 | 80 | 48 | 52 |
| 84.0 | 3 | 40 | 81 | 70 | 30 |
| 88.7 | 2 | 0 | 89 | 83 | 17 |
| 93.5 | 2 | 0 | 90 | 90 | 10 |
| 97.8 | 2 | 0 | 91 | 92 | 8 |

[a] By n.m.r. analysis of the crude reaction products obtained by treating (for the time and at the temperature stated) 0.25 g of substrate with 0.1 ml of $HNO_3$ (*d* 1.42) and 3 ml of $H_2SO_4$. The reaction mixture was quenched with water and the crude product dried and analysed by n.m.r. in $CDCl_3$ at 100 MHz.

## EXPERIMENTAL

*Preparation of Compounds.*—The following isoxazoles were prepared by the literature methods quoted: 3-methyl-5-phenyl- [10] (5) (63%), m.p. 64—66° (lit.,[10] 65.5—66°), 5-methyl-3-phenyl- [11] (6) (44%), m.p. 39—41° (lit.,[11] 41—42°), and 3-methyl-5-*p*-nitrophenyl-isoxazole [7] (15) (58%) (a lower temperature, 5 °C, was used), m.p. 183—185° (lit.,[7] 180°).

*5-Methyl-3-m-nitrophenylisoxazole* (18).—Pre-mixed $HNO_3$ (*d* 1.42; 0.25 ml) and $H_2SO_4$ (*d* 1.84; 1 ml) were added

[9] S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, *J.C.S. Perkin II*, 1974, 399.
[10] M. Ceresole, *Ber.*, 1884, **17**, 812.
[11] B. Eistert and E. Merkel, *Chem. Ber.*, 1953, **86**, 915.

TABLE 3

Absorption maxima (nm) and p$K_a$ data for substituted isoxazoles and isoxazolium salts [a]

| | Substituent at position | | | | $\lambda_{max.}$ (log ε) | | | Basicity | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Compd. | 2 | 3 | 4 | 5 | Neutral species [b] | Cationic species [c] | λ [d] | λ [e] | $H_0^{(1/2)}$ | $m$ | p$K_a$ |
| (5) | | Me | H | Ph | 261 (4.26) | 287 (4.33) | 310,[f] 325 [g] | 289 | −2.30 | 0.99 | −2.28 |
| (6) | | Ph | H | Me | 241 (4.17) | 275 (4.28) | 250 | 276 | −2.50 | 0.84 | −2.10 |
| (8) | Me | Me | H | Ph | | 284 (4.31),[b] 289 (4.32) | 315,[f] 325 [g] | | | | |
| (10) | Me | Ph | H | Me | | 263 (4.15),[b] 268 (4.14) | 250 | | | | |
| (12) | Me | Me | H | *p*-$NO_2$·$C_6H_4$ | | 295 (4.38),[b] 302 (4.37) | | | | | |
| (14) | Me | *m*-$NO_2$·$C_6H_4$ | H | Me | | 252 (4.49),[b] 255 (4.46) | | | | | |
| (15) | | Me | H | *p*-$NO_2$·$C_6H_4$ | 310 (4.08) | 298 (4.33) | | 295 | −2.70 | 0.95 | −2.57 |
| (16) | | Me | $NO_2$ | *p*-$NO_2$·$C_6H_4$ | 300 (3.96) | 293 (4.22) | | 290 | −7.16 | 0.87 | −6.23 |
| (17) | | *p*-$NO_2$·$C_6H_4$ | H | Me | 286 (4.08) | 284 (4.24) | 250 | 275 | −3.91 | 0.89 | −3.48 |
| (18) | | *m*-$NO_2$·$C_6H_4$ | H | Me | 231 (4.35) | 262 (4.41) | | 265 | −3.07 | 0.87 | −2.67 |
| (19) | | *p*-$NO_2$·$C_6H_4$ | $NO_2$ | Me | 268 (4.18) | 275 (4.20) | | 260 | −8.20 | 0.87 | −7.13 |

[a] As perchlorate salts. [b] Measured in 5M-$H_2SO_4$ ($H_0$ *ca.* 0.05). [c] Measured in 98% $H_2SO_4$ ($H_0$ *ca.* −10.5). [d] λ For study of nitration kinetics. [e] λ For p$K_a$. [f] λ For low acidity. [g] λ For high acidity.

dropwise to 5-methyl-3-phenylisoxazole (0.57 g) in $H_2SO_4$ (*d* 1.84; 5 ml) and, after 1 h at 0—5 °C, poured onto ice. The *isoxazole* crystallised from EtOH as prisms (57%), m.p. 123—125° (Found: C, 59.1; N, 13.7; H, 4.0. $C_{10}H_8N_2O_3$ requires C, 58.8; N, 13.7; H, 3.9%).

5-*Methyl*-3-p-*nitrophenylisoxazole* (17).—The previous experiment was carried out using $H_2SO_4$ (70% w/w), at 100 °C for 5 days. The p-*nitrophenyl* derivative crystallised from EtOH as needles (21%), m.p. 157—159° (Found: C, 58.7; N, 13.7; H, 3.8. $C_{10}H_8N_2O_3$ requires C, 58.8; N, 13.7; H, 3.9%).

3-*Methyl*-4-*nitro*-5-p-*nitrophenylisoxazole* (16).—Fuming $HNO_3$ (3 ml) was added dropwise to 3-methyl-5-*p*-nitrophenylisoxazole (0.5 g) in $Ac_2O$ (5 ml) and the mixture was kept at 75 °C for 4 days. The cooled solution was neutralized (N-NaOH) and the precipitated *isoxazole* crystallised from EtOH as prisms (12%), m.p. 153—155° (Found: C, 47.9; N, 16.8; H, 2.9. $C_{10}H_7N_3O_5$ requires C, 48.2; N, 16.9; H, 2.8%).

5-*Methyl*-4-*nitro*-3-p-*nitrophenylisoxazole* (19).—This compound was prepared as described above for the 5-*p*-nitrophenyl isomer except that a high temperature (100 °C) was used. Crystallisation from MeOH gave the *isoxazole* as prisms (10%), m.p. 162—164° (Found: C, 47.9; N, 17.0; H, 3.0. $C_{10}H_7N_3O_5$ requires C, 48.2; N, 16.9; H, 2.8%).

2,3-*Dimethyl*-5-*phenylisoxazolium Toluene*-p-*sulphonate*.—Isoxazole (5) (1.56 g) and methyl toluene-*p*-sulphonate (1.85 g) were heated at 80 °C for 20 h; the mixture was cooled and dissolved in hot EtOH, and the solution filtered and evaporated to give the *tosylate*, which crystallised from ethanol–ethyl acetate as needles (61%), m.p. 156—159° (Found: C, 60.3; N, 4.0; H, 5.4. $C_{18}H_{19}NO_4S$ requires C, 62.6; N, 4.0; H, 5.5%).

2,3-*Dimethyl*-5-p-*nitrophenylisoxazolium Toluene*-p-*sulphonate*.—Compound (15) (0.16 g) and methyl toluene-*p*-sulphonate (0.5 g) were heated under reflux in tetrahydrofuran (15 ml) for 48 h. The mixture was evaporated and the *tosylate* separated from ethanol–ether as needles (46%), m.p. 139—141° (Found: C, 52.0; N, 6.5; H, 4.4. $C_{18}H_{18}N_2O_6S$ requires C, 51.7; N, 6.7; H, 4.3%).

2,5-*Dimethyl*-3-*phenylisoxazolium Trifluoromethanesulphonate*.—Methyl trifluoromethanesulphonate (0.6 ml) and (6) (0.8 g) in dry benzene (3 ml) at 20 °C for 24 h, gave the *methotrifluoromethanesulphonate* as plates (78%), m.p. 98—100° (Found: C, 44.2; H, 4.0; N, 4.7. $C_{12}H_{12}F_3NO_4S$ requires C, 44.6; H, 3.7; N, 4.3%).

Prepared similarly was 2,5-*dimethyl*-3-*nitrophenylisoxazolium trifluoromethanesulphonate* as pale yellow plates

TABLE 4

Kinetics of nitration of substituted isoxazoles and isoxazolium salts in the high acidity region

| % $H_2SO_4$ | $-H_0$ [a] | −log $k_2$(obs) | −log $k_2^m$ [b] | −log $k_2^p$ |
|---|---|---|---|---|
| 3-Methyl-5-phenylisoxazole (5) (20 °C) | | | | |
| 82.08 | 7.92 | 1.166 | | 1.17 |
| 83.94 | 8.21 | 0.285 | | 0.29 |
| 84.17 | 8.25 | 0.249 | | 0.25 |
| 85.56 | 8.49 | −0.276 | | −0.28 |
| 87.02 | 8.73 | −0.464 | | −0.46 |
| 88.77 | 8.96 | −0.703 | | −0.70 |
| 91.55 | 9.39 | −0.865 | | −0.87 |
| 93.64 | 9.73 | −0.558 | | −0.56 |
| 95.21 | 9.94 | −0.497 | | −0.50 |
| 97.41 | 10.44 | −0.336 | | −0.34 |
| 5-Methyl-3-phenylisoxazole (6) (20 °C) | | | | |
| 83.24 | 8.11 | 1.823 | 2.32 | 2.27 |
| 85.57 | 8.49 | 1.093 | 1.52 | 1.70 |
| 86.44 | 8.64 | 0.929 | 1.34 | 1.58 |
| 87.25 | 8.74 | 0.681 | 1.08 | 1.37 |
| 88.89 | 8.98 | −0.335 | 0.04 | 0.49 |
| 92.75 | 9.56 | −0.285 | 0.07 | 0.67 |
| 94.75 | 9.89 | −0.011 | 0.33 | 1.03 |
| 96.01 | 10.10 | 0.140 | 0.48 | 1.21 |
| 97.36 | 10.43 | 0.255 | 0.59 | 1.38 |
| 2,3-Dimethyl-5-phenylisoxazolium perchlorate (8) (20 °C) | | | | |
| 82.10 | 7.92 | 1.078 | | 1.08 |
| 84.17 | 8.25 | −0.044 | | −0.04 |
| 85.56 | 8.49 | −0.427 | | −0.43 |
| 85.80 | 8.54 | −0.345 | | −0.35 |
| 87.01 | 8.73 | −0.781 | | −0.78 |
| 88.77 | 8.96 | −1.051 | | −1.05 |
| 91.54 | 9.39 | −1.241 | | −1.24 |
| 93.64 | 9.73 | −0.998 | | −1.00 |
| 95.22 | 9.94 | −1.068 | | −1.07 |
| 97.41 | 10.44 | −0.752 | | −0.75 |
| 2,5-Dimethyl-3-phenylisoxazolium perchlorate (10) (20 °C) | | | | |
| 83.53 | 8.15 | 2.116 | 2.42 | |
| 85.83 | 8.54 | 1.188 | 1.49 | |
| 86.69 | 8.68 | 0.629 | 0.93 | |
| 87.48 | 8.79 | 0.575 | 0.88 | |
| 88.89 | 8.98 | −0.095 | 0.21 | |
| 92.76 | 9.56 | 0.037 | 0.34 | |
| 94.67 | 9.87 | 0.333 | 0.63 | |
| 97.37 | 10.43 | 0.293 | 0.59 | |

[a] $H_0$ Values are corrected (C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654) for temperature. [b] $k_2$ Values were divided by 2 to allow for the statistical factor at the *meta*-position.

(36%) (from benzene), m.p. 150—152° (Found: C, 38.7; N, 7.8; H, 3.2. $C_{12}H_{11}F_3N_2O_6$ requires C, 39.1; N, 7.6; H, 3.0%).

2,3-*Dimethyl-5-phenylisoxazolium Perchlorate.*—Perchloric acid (73%; 0.5 ml), the tosylate (0.31 g), and water (10 ml) were mixed to give the *perchlorate* as prisms (80%), m.p. 185—188° (from ethanol) (Found: C, 48.4; N, 5.0; H, 4.4. $C_{11}H_{12}ClNO_5$ requires C, 48.3; N, 5.1; H, 4.4%).

R12) with sample spinning. Tetramethylammonium sulphate was used as internal standard ($\tau$ 6.81) for solutions in $D_2SO_4$, otherwise $Me_4Si$ was used. U.v. spectra (Table 3) were determined with a Unicam SP 800A self-recording instrument; individual optical densities were recorded in Spectrosil 10 mm silica cells using a Unicam SP 500 instrument. p$K$ Values (Table 3) were measured by the u.v method.[12]

TABLE 5

Kinetics of nitration of substituted isoxazoles and isoxazolium salts in the low acidity region

| % $H_2SO_4$ | $-H_0$ [a] | $-(H_R + \log a_{H_2O})$ [b] | $-\log k_2$(obs) | $-\log k_2^m$ [c] | $-\log k_2^p$ |
|---|---|---|---|---|---|
| 3-Methyl-5-phenylisoxazole (5) (40 °C) | | | | | |
| 71.07 | 5.74 | 12.78 | 4.077 | | 4.08 |
| 72.63 | 5.96 | 13.20 | 3.698 | | 3.70 |
| 73.53 | 6.12 | 13.42 | 3.423 | | 3.42 |
| 75.24 | 6.38 | 13.88 | 2.845 | | 2.85 |
| 76.18 | 6.54 | 14.16 | 2.477 | | 2.48 |
| 77.73 | 6.77 | 14.58 | 1.891 | | 1.89 |
| 78.35 | 6.87 | 14.79 | 1.815 | | 1.82 |
| 5-Methyl-3-phenylisoxazole (6) (20 °C) | | | | | |
| 73.69 | 6.51 | 14.48 | 3.202 | 4.33 | 3.28 |
| 75.57 | 6.79 | 15.04 | 2.798 | 3.80 | 2.90 |
| 76.71 | 6.99 | 15.39 | 2.603 | 3.53 | 2.72 |
| 77.88 | 7.21 | 15.80 | 2.448 | 3.31 | 2.59 |
| 79.15 | 7.40 | 16.33 | 2.158 | 2.94 | 2.33 |
| 81.40 | 7.81 | 17.15 | 1.757 | 2.38 | 2.04 |
| 2,3-Dimethyl-5-phenylisoxazolium perchlorate (8) (50 °C) | | | | | |
| 73.23 | 5.72 | 12.40 | 3.537 | | 3.58 |
| 75.10 | 6.17 | 12.88 | 2.821 | | 2.82 |
| 76.71 | 6.43 | 13.36 | 2.406 | | 2.41 |
| 77.29 | 6.52 | 13.54 | 2.052 | | 2.05 |
| 78.10 | 6.64 | 13.78 | 1.674 | | 1.67 |
| 79.17 | 6.80 | 14.10 | 1.249 | | 1.25 |
| 2,5-Dimethyl-3-phenylisoxazolium perchlorate (10) (40 °C) | | | | | |
| 75.58 | 6.41 | 13.98 | 2.656 | 2.96 | |
| 76.71 | 6.55 | 14.29 | 2.404 | 2.71 | |
| 77.88 | 6.80 | 14.64 | 2.204 | 2.51 | |
| 79.15 | 6.95 | 15.08 | 1.657 | 1.96 | |
| 81.43 | 7.30 | 15.93 | 1.012 | 1.31 | |

[a] See footnote *a* to Table 4. [b] $H_R$ values are corrected (M. J. Cook, N. L. Dassanayake, C. D. Johnson, A. R. Katritzky, and T. W. Toone, *J. Amer. Chem. Soc.*, 1975, **97**, 760 for temperature. [c] $k_2$ Values were divided by 2 to allow for the statistical factor at the *meta*-position.

2,3-*Dimethyl*-5-p-*nitrophenylisoxazolium Perchlorate.*—The tosylate (0.47 g) in deionised water (40 ml) was passed down a column of Amberlite IRA-400 resin (perchlorate form) and the eluate was evaporated to give the *perchlorate* (83%), which crystallised from ethanol as needles, m.p. 204—207° (Found: C, 41.2; N, 9.1; H, 3.6. $C_{11}H_{11}ClN_2O_7$ requires C, 41.4; N, 8.8; H, 3.5%).

Similarly the trifluoromethanesulphonate (0.77 g), $HClO_4$ (73%; 0.25 ml), and deionised water (4 ml) gave 2,5-*dimethyl*-3-*phenylisoxazolium perchlorate* as prisms (84%), m.p. 150—152° (from ethanol) (Found: C, 47.8; N, 5.1; H, 4.4. $C_{11}H_{12}ClNO_5$ requires C, 48.3; N, 5.1; H, 4.4%); and trifluoromethanesulphonate (0.09 g), $HClO_4$ (0.03 ml), and deionised water (2 ml) gave 2,5-*dimethyl*-3-m-*nitrophenylisoxazolium perchlorate* as prisms (43%) (from ethanol), m.p. 162—164° (Found: C, 39.6; N, 8.6; H, 3.5. $C_{11}H_{11}ClN_2O_7$ requires C, 41.5; N, 8.8; H, 3.5%).

*Spectroscopy.*—N.m.r. spectra (Table 1) were recorded at 100 MHz (Varian HA-100) or at 60 MHz (Perkin-Elmer

[12] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.

*Kinetics.*—The method is described elsewhere (*cf.* refs. 13 and 14). Results are recorded in Tables 4 and 5.

## RESULTS AND DISCUSSION

Rate profiles for the high (Figure 1) and low (Figure 2) acidity regions were constructed from the kinetic data of Tables 4 and 5. For 5-methyl-3-phenylisoxazole, where nitration occurs at both the *meta*- and *para*-positions in a ratio which depends on the acidity, the individual rate profiles were constructed for reaction at each position, using the data of Table 2 (with interpolation) to calculate individual rates for each position (see Tables 4 and 5). An implicit assumption in this procedure is that isomer proportions do not change markedly with temperature.

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

[14] A. G. Burton, A. R. Katritzky, M. Konya, and H. O. Tarhan, *J.C.S. Perkin II*, 1974, 389.

*Determination of Species undergoing Reaction.*—In the high acidity region the methyl cations (8) and (10)

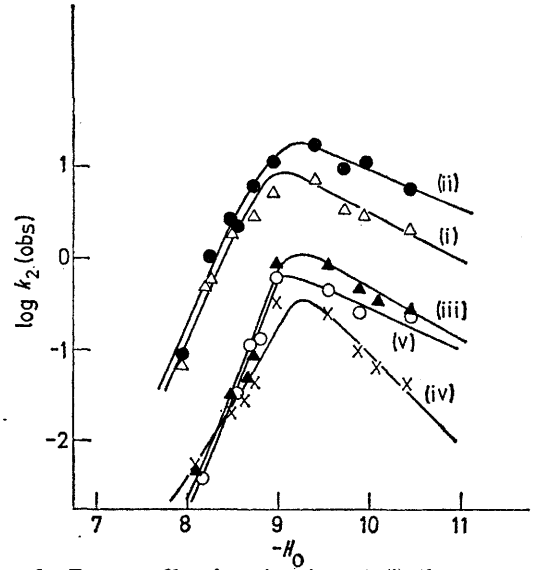



FIGURE 1 Rate profiles for nitration at (i) the *para*-position of 3-methyl-5-phenylisoxazole at 20 °C; (ii) the *para*-position of 2,3-dimethyl-5-phenylisoxazolium perchlorate at 20 °C; (iii) the *meta*-position and (iv) the *para*-position of 5-methyl-3-phenylisoxazole at 20 °C; and (v) the *meta*-position of 2,5-dimethyl-3-phenylisoxazolium perchlorate at 20 °C

disclose slopes (Table 6) of 0.43—0.55, values characteristic [13] of majority species reactions, as expected. The acid. However, the slope for reaction of 5-methyl-3-phenylisoxazole (6) at the *para*-position (0.82) is significantly higher and suggests [13] reaction *via* the minority free base species.

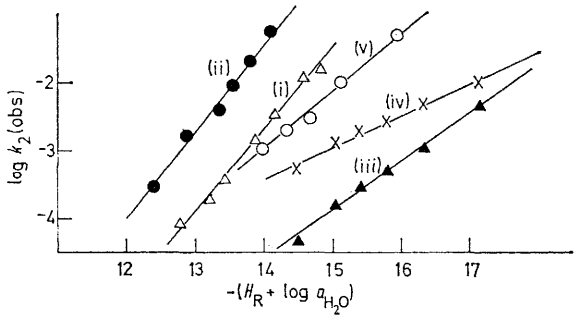



FIGURE 2 Moodie–Schofield plots for nitration at (i) the *para*-position of 3-methyl-5-phenylisoxazole at 40 °C; (ii) the *para*-position of 2,3-dimethyl-5-phenylisoxazolium perchlorate at 50 °C; (iii) the *meta*-position and (iv) the *para*-position of 5-methyl-3-phenylisoxazole at 20 °C; and (v) the *meta*-position of 2,5-dimethyl-3-phenylisoxazolium perchlorate at 40 °C

These conclusions are confirmed by the rate profile slopes in the low acidity region (Table 6). On the basis of the Moodie–Schofield criterion [15] the slopes are all above 0.7 except for reaction of (6) at the *para*-position for which the low slope of 0.45 indicates reaction *via* a minority species. Using the $d[\log k_2(obs)]/d(-H_0)$ criterion [16] we find slopes of >1.8 except for (6) which gives a slope of 0.94 for the *para*-position, which leads

TABLE 6

Rate profile slopes

| | | Low acidity | | | | High acidity region (91—98% $H_2SO_4$) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Slope | | | | | |
| Compound | Position of nitration | $T$/°C | $a$ | $b$ | Species reacting [d] | $T$/°C | Slope [c] | Species reacting [d] |
| (5) | *para* | 40 | 1.19 | 2.09 | C.A. | 20 | 0.49 | C.A. |
| (6) | *meta* | 20 | 0.71 | 1.47 | C.A. | 20 | 0.60 | C.A. |
| (8) | *para* | 50 | 1.32 | 2.13 | Cation | 20 | 0.43 | Cation |
| (10) | *para* | 20 | 0.45 | 0.94 | F.B. | 20 | 0.82 | F.B. |
| | *meta* | 40 | 0.86 | 1.86 | Cation | 20 | 0.55 | Cation |

[a] $d[\log k_2(obs)]/d[-(H_R + \log a_{H_2O})]$, correlation coefficients were ≥0.996 except for (6) in the *para*-position with $r = 0.991$. [b] $d[\log k_2(obs)]/d(-H_0)$, correlation coefficients were all ≥0.983. [c] $d[\log k_2(obs)]/d(-H_0)$. [d] C.A. = conjugate acid; F.B. = free-base.

TABLE 7

Standard rate constants [a]

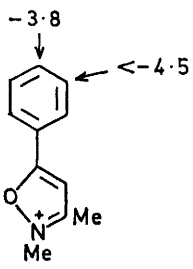
| Compound | Position of nitration | $T$/°C | Range ($H_0$) | $\frac{d(\log k_2)}{d(-H_0)}$ | $\log k_2$ (at $H_0 - 6.6$) | $\log k_2$ (25 °C) | Species | $\log k_2^0$ |
|---|---|---|---|---|---|---|---|---|
| (5) | *para* | 40 | 5.7—6.9 | 2.09 | −2.345 | −3.574 | + | −3.57 |
| (6) | *meta* | 20 | 6.5—7.8 | 1.47 | −4.143 [b] | −3.705 [b] | + | −3.71 [b] |
| | *para* | 20 | 6.5—7.8 | 0.93 | −3.126 | −2.688 | 0 | 0.76 [c] |
| (8) | *para* | 50 | 5.7—6.8 | 2.09 | −1.830 | −3.816 | + | −3.82 |
| (10) | *meta* | 40 | 6.4—7.3 | 1.85 | −2.666 [b] | −3.895 [b] | + | −3.90 [b] |

[a] See ref. 16. [b] $k_2$ Values were divided by 2 to allow for the statistical factor at the *meta*-position. [c] Calculated using $pK_a$ value.

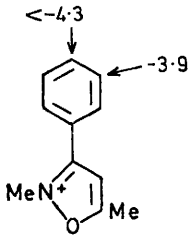
slopes for reaction of 3-methyl-5-phenylisoxazole (5) at the *para*-position and for 5-methyl-3-phenylisoxazole (6) at the *meta*-position of 0.49 and 0.62, respectively, are similar to those of their model compounds, and again indicate reaction *via* the majority species, the conjugate to the same conclusion; [16] the slope of 1.47 for the *meta*-position of (6) lies at the borderline.

[15] J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, 'Nitration and Aromatic Reactivity,' Cambridge University Press, 1971, p. 147.

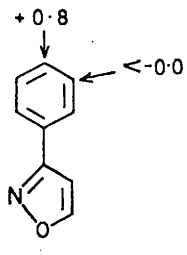
*Standard Nitration Rates.*—Using the previously justified procedure,[16] we have calculated (Table 7) standard rate constants for nitration applicable to $H_0$ —6.6 and 25 °C. The data show that a benzene ring is clearly deactivated towards nitration by a positively charged isoxazolin-3- or -5-yl substituent. Using the data in Table 2, the pattern of deactivation of (20), (21), and (22) may be deduced: we deduce maximum rates for the nitration in the other positions by assuming that 20% of isomer formation would have been noticed.




(20)

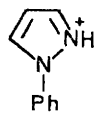



(21)

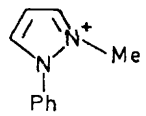



(22)

An isoxazolin-5-io-substituent (20) specifically deactivates the *meta*-position more than the *para*-position —evidently the strong inductive electron withdrawal is partly counterbalanced by mesomeric electron donation, and this group behaves analogously to a halogen, and to pyrazolin-1-io (23),[14] the 2-methyl analogue (24),[14] and




(23)




(24)

various 3-oxo- [17] and 5-oxo-pyrazolin-1-yls.[18] In magnitude the deactivation is considerably greater than that caused by Cl (log $k_2^0$ 0.30) but not so great as that of $NH_3^+$ (log $k_2^0$ —5.0 at the 4-position).[16]

An isoxazolin-3-io-group (21) specifically deactivates the *para*-position more than the *meta*-; the proximity of the positively charged nitrogen atom causes this group to behave like the well known π-electron-withdrawing substituents. In magnitude the deactivation is a little greater than that of the neutral acetyl group for which log $k_2^0 = -3.2$.[16]

By contrast the neutral group, isoxazol-3-yl (22) again specifically deactivates the *meta*-position. At the *para*-position, the rate is close to that for benzene itself (log $k_2^0$ +1.2).[16]

[5/306 *Received*, 14*th February*, 1975]

[16] A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1600.

[17] M. Dereli, A. R. Katritzky, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1609.

[18] A. G. Burton, M. Dereli, A. R. Katritzky, and H. O. Tarhan, *J.C.S. Perkin II*, 1974, 382.