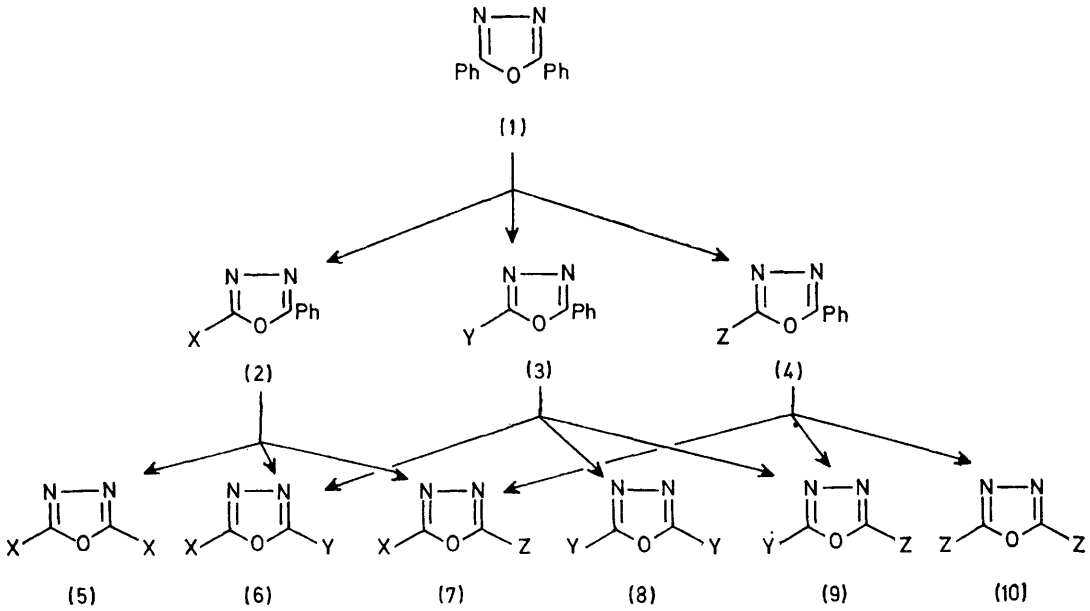
Substitution Reactions of Phenylated Aza-heterocycles. Part 1. Nitration of 2,5-Diphenyl-1,3,4-oxadiazole: a Product Study using High Performance Liquid Chromatography

By **Alexander Blackhall** and **Donald L. Brydon**, I.C.I. Fibres, Hookstone Road, Harrogate, Yorkshire HG2 8QN
Anthony J. G. Sagar and **David M. Smith**,* Department of Chemistry, University of St. Andrews, Purdie Building, St. Andrews, Fife KY16 9ST

Contrary to a previous literature report, nitration of 2,5-diphenyl-1,3,4-oxadiazole (1) under various conditions gives a mixture of all six possible 2,5-bisnitrophenyl derivatives, which may be analysed quantitatively using high performance liquid chromatography. Nitration using nitric acid alone gives mainly the three isomers with *p*-nitrophenyl groups, *i.e.* (7), (9), and (10), whereas mixed acids and nitronium tetrafluoroborate give mainly *meta*-nitration products, *i.e.* (6), (8), and (9). Nitration of the three 2-(nitrophenyl)-5-phenyl-1,3,4-oxadiazoles [*i.e.* the second stage of the nitration of (1)] also shows considerable variation of product ratio according to the conditions.

ALTHOUGH electrophilic aromatic substitution is among the most extensively studied organic reactions, relatively little attention appears to have been paid to electrophilic substitution in a benzene ring bearing a heteroaromatic substituent. Of the recorded examples of such reactions, the majority are nitrations,[1,2] but very few of these have been studied in detail, and there are (as yet) no reliable guidelines to enable one to predict the ' directive effects ' of heteroaromatic substituents.

A major difficulty in this field has been the finding of a satisfactory method for the analysis of the (often complex) mixtures which are produced in these reactions. If the products are volatile (as in the nitration of 2-phenylpyridine [3]) they may be amenable to g.l.c. analysis. In other cases (*e.g.* the nitration of 4-phenylpyridine [4]) spectroscopic methods may be used. We have been able to show, in several instances, that high performance liquid chromatography (h.p.l.c.) may be used to considerable advantage in studies of this kind, a point which we now illustrate with reference to the nitration of 2,5-diphenyl-1,3,4-oxadiazole (1).



X = *o* - $NO_2C_6H_4$
Y = *m* - $NO_2C_6H_4$
Z = *p* - $NO_2C_6H_4$

This nitration has been investigated previously, by Grekov and Azen.[5] According to these authors, nitration of (1), using fuming nitric acid (*d* 1.51) alone, gives a mixture from which the three symmetrical dinitro-isomers (5), (8), and (10) may be isolated by fractional crystallisation in yields of 40, 20, and 27%, respectively.† On the other hand, nitration with fuming nitric acid in

† The percentage yields in Grekov and Azen's paper appear to have been miscalculated. If the weights of products are taken to be correct, the percentages ought to be as follows: 34, 17, and 24% for (5), (8), and (10); 30 and 32% for (3) and (8).

presence of concentrated sulphuric acid allegedly gives a preponderance of *meta*-nitrated products, both the mononitro-derivative (3) and the dinitro-derivative (8) being obtained (yield **31** and **38**%, respectively *).

It does not, of course, make sense that only the symmetrical dinitro-compounds should be formed by nitration of (1) in fuming nitric acid: if *ortho*-, *meta*-, and *para*-nitration all occur to a significant extent, as Grekov and Azen claim, the mixture should also contain appreciable amounts of the unsymmetrical dinitro-isomers (6), (7), and (9). Moreover, unless this nitration is selective to a remarkable degree, it is difficult to envisage how the three symmetrical products could possibly account for 75% of the total product, as the paper suggests. Accordingly, we have re-investigated the nitration of (1) under both sets of conditions described by Grekov and Azen, and, perhaps not surprisingly, we have been unable to reproduce their results in either case.

With fuming nitric acid alone as nitrating agent, the bis-*p*-nitrophenyl compound (10) may indeed be obtained, as Grekov and Azen indicate, by fractional crystallisation of the crude product, but h.p.l.c. analysis of the mother liquors shows the presence of five other compounds in addition to (10), and attempts to obtain the other isomers (5) and (8) according to the Soviet authors' instructions give solids which, from their m.p.s and h.p.l.c. analyses, are undoubtedly mixtures. With fuming nitric acid and concentrated sulphuric acid, the same six products are obtained [although the proportion of compound (10) is very small], and we have failed to isolate either (3) or (8) by following Grekov and Azen's method. We have also shown that the published reaction conditions are unnecessarily severe: the nitrations are essentially complete after 2—3 h at 0°, and the product ratios are unaffected by higher temperatures or longer reaction times.

Comparison with authentic samples, using h.p.l.c., has established beyond doubt that the six reaction products are, as expected, the six dinitro-compounds (5)—(10),

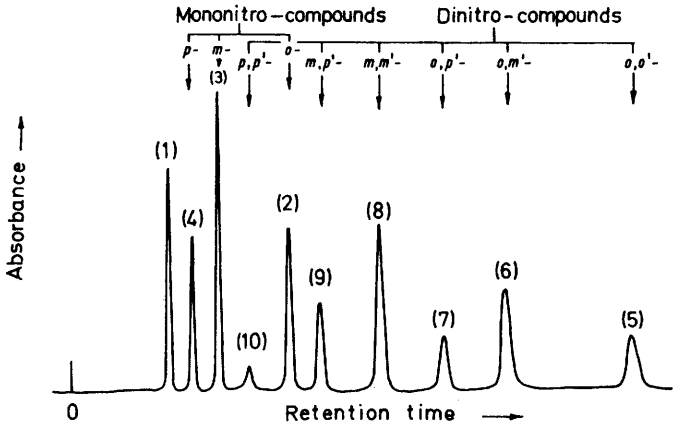


FIGURE 1 H.p.l.c. separation of 2,5-diphenyl-1,3,4-oxadiazole (1) and its nitration products

* The percentage yields in Grekov and Azen's paper appear to have been miscalculated. If the weights of products are taken to be correct, the percentages ought to be as follows: **34**, **17**, and 24% for (5), (8), and (10); **30** and **32**% for (3) and (8).

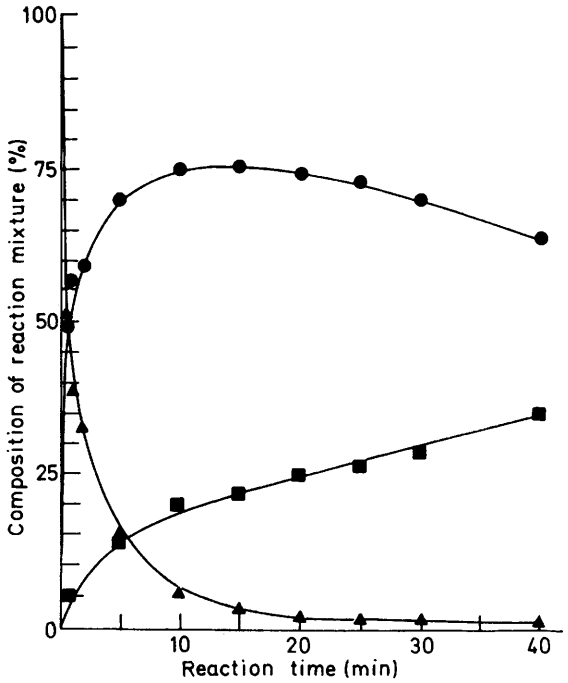


FIGURE 2 Nitration of 2,5-diphenyl-1,3,4-oxadiazole with fuming nitric acid: ▲, starting compound (1); ●, mixture of mononitro-compounds; ■, mixture of dinitro-compounds

and that no mononitro-compound is present in either mixture. Indeed, 2,5-diphenyl-**1**,**3**,4-oxadiazole and its mono- and dinitro-derivatives may be separated so cleanly by h.p.l.c. (*cf.* Figure 1) that quantitative analysis of the product mixtures is relatively simple. The isomer ratios obtained in these nitrations are shown in Table 1, along with those obtained from the nitration of (1) using nitronium tetrafluoroborate in sulpholan.

TABLE 1

Nitration of 2,5-diphenyl-1,3,4-oxadiazole (1)

	Isomer ratio (%)					
Nitrating agent	(5)	(6)	(7)	(8)	(9)	(10)
HNO_3 (*d* 1.5)	5	15	29	7	24	21
$HNO_3 + H_2SO_4$	5	26	12	25	27	6
$NO_2^+BF_4^-$	11	27	18	20	20	4

The h.p.l.c. method may also be used to follow the progress of the reactions, and we have studied the nitration, using nitric acid alone, in this way (see Figure 2). Mononitration of 2,5-diphenyl-**1**,**3**,4-oxadiazole occurs very rapidly, the maximum yield of mononitro-compounds (75%; *o* 15%, *m* 23%, *p* 37%) being attained after only 10 min. The second nitration appears to occur much more slowly.

Whether or not this *o* : *m* : *p* ratio is an accurate reflection of the relative reactivities of these positions towards nitration depends, of course, on the relative rates at which the three isomers (2)—(4) are consumed, *i.e.* are nitrated further, and to date we have not obtained an accurate measure of these rates. We have, however, determined the ratios of isomeric dinitro-compounds produced by nitration of compounds (2)—(4), and these are set out in Tables 2—4.

If it can be assumed in every case that the dinitration

TABLE 2

Nitration of 2-*o*-nitrophenyl-5-phenyl-1,3,4-oxadiazole (2)

	Isomer ratio (%)		
Nitrating agent	(5)	(6)	(7)
HNO_3 (*d* 1.5)	19	34	47
$HNO_3 + H_2SO_4$	15	67	18
$NO_2^+BF_4^-$	39	20	41

TABLE 3

Nitration of 2-*m*-nitrophenyl-5-phenyl-1,3,4-oxadiazole (3)

	Isomer ratio (%)		
Nitrating agent	(6)	(8)	(9)
HNO_3 (*d* 1.5)	26	29	45
$HNO_3 + H_2SO_4$	22	60	18
$NO_2^+BF_4^-$	35	36	29

TABLE 4

Nitration of 2-*p*-nitrophenyl-5-phenyl-1,3,4-oxadiazole (4)

	Isomer ratio (%)		
Nitrating agent	(7)	(9)	(10)
HNO_3 (*d* 1.5)	34	23	43
$HNO_3 + H_2SO_4$	22	60	18
$NO_2^+BF_4^-$	50	19	30

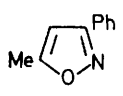
of 2,5-diphenyl-1,3,4-oxadiazole (1) consists of two nitration steps which are consecutive rather than concurrent, the isomer ratios in Tables 2—4 correspond to those of the second nitration of (1). The data in these Tables may be taken together with those in Table 1 to provide isomer ratios for the mononitration of (1) which, although approximate, are within the limit of experimental error. These ratios are shown in Table 5.

TABLE 5

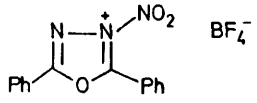
Mononitration of 2,5-diphenyl-1,3,4-oxadiazole (results calculated from the data in Tables 1–4)

	Isomer ratio (%)		
Nitrating agent	(2)	(3)	(4)
HNO_3 (*d* 1.5)	25	25	50
$HNO_3 + H_2SO_4$	26	41	33
$NO_2^+BF_4^-$	29	58	13

Mechanistic interpretation of these results is clearly not a simple matter. 2,5-Diaryl-1,3,4-oxadiazoles are very weak bases, with pK_a values between −1 and −3,* and as such they may be expected to undergo nitration either as free bases or as the conjugate acids, depending on the reaction conditions. It is already known [8] that 5-methyl-3-phenylisoxazole (11), pK_a −2.10, undergoes *meta*- and *para*-nitration in nitric–sulphuric acid mixtures, and it has been shown that the *meta*-nitration involves the conjugate acid whereas the *para*-nitration occurs on the free base. In trying to explain the isomer ratios obtained on dinitration of 2,5-diphenyl-1,3,4-oxadiazole, therefore, it is tempting to suggest that the nitration in fuming nitric acid alone [which gives a preponderance of the *para*-nitrated compounds (7), (9), and (10)] may involve the free base, whereas the nitration in mixed acids [which gives predominantly the products of *meta*-nitration, (6), (8), and (9)] may involve the diphenyloxadiazolium cation. These *meta*-nitrated compounds are also the principal products of dinitration of (1) using nitronium tetrafluoroborate (Table 1), and although this reaction is unlikely to involve the conjugate acid of (1), it may well involve the *N*-nitro-oxadiazolium cation (12). The involvement of (12) may also account for the enhanced proportions of *ortho*-nitrated products in these reactions, since the nitro-group may be transferred intramolecularly from the heteroatom to the adjacent *ortho*-carbon (*cf.* the nitration of 4-phenylpyrimidine [9]).



(11)



(12)

Intuitively, however, it seems rather improbable that a simple theory, such as the above, will prove adequate to explain such a complex set of reactions. For example, although very similar product ratios are obtained in the dinitration of (1) with mixed acids and with nitronium tetrafluoroborate, it does not necessarily follow that the two reactions involve similar mechanisms. The predominant *meta*-nitration pattern observed in the final product mixture is achieved mainly in the first nitration stage using the fluoroborate (Table 5) and mainly in the second nitration stage using mixed acids (Tables 2—4). Also we cannot exclude the possibility that 2,5-diaryl-1,3,4-oxadiazoles may be diprotonated in strongly acid media [although we have been unable to repeat Grekov and Azen's preparation of a ' double sulphate ' of (1)].

Experiments to assist in the elucidation of the mechanisms are now in progress, and we shall report the results of these in due course.

EXPERIMENTAL

1,2-*Diaroylhydrazines*.—(a) Dibenzoylhydrazine was obtained (yield 70%) from benzoyl chloride, hydrazine sulphate, and sodium hydroxide by the published method: [10] it had m.p. 232—234° (lit., 234—238°).

(b) *p*-Nitrobenzoyl chloride (8 g) was added gradually, with cooling, to a stirred solution of hydrazine hydrate (1 g) and anhydrous sodium carbonate (2.33 g) in dimethylformamide (50 ml). After 4 h the mixture was added to water (50 ml), and the product was filtered off, washed with methanol, and recrystallised from dimethylformamide–acetic acid. 1,2-Bis-(*p*-nitrobenzoyl)hydrazine (2.75 g, 42%) had m.p. 294—296° (lit., [11] 296—297°). 1,2-Bis-(*m*-nitrobenzoyl)hydrazine, m.p. 240—242° (lit.,[11] 245, lit.,[12] 242°) and 1,2-bis-(*o*-nitrobenzoyl)hydrazine, m.p. 296—297° (lit.,[13] 298°), were similarly prepared (yields 40 and 47% respectively).

(c) Unsymmetrically substituted diaroylhydrazines were obtained by reaction of equimolar quantities of the appropriate monoaroylhydrazine and aroyl chloride in presence of sodium carbonate (an adaptation of the procedure of Frost *et al.*[11]). [*p*-Nitrobenzoylhydrazine, m.p. 209—210° (from water) (lit.,[12] 210°) was prepared from ethyl *p*-nitrobenzoate (52 g) and hydrazine hydrate (40 g; 3-fold excess) by boiling in ethanol (80 ml) for 1 h, yield 42.1 g (87%). *m*-Nitro-

* The literature pK_a values [6] for 2,5-diphenyl-1,3,4-oxadiazole are −0.28 and −0.32, but our estimate using a spectrophotometric method [7] is *ca.* 1 p*K* unit lower. We shall discuss the basicities of 2,5-diaryl-1,3,4-oxadiazoles fully in a subsequent paper.

TABLE 6

Unsymmetrical 1,2-diaroylhydrazines from the reaction

$XC_6H_4CONHNH_2 + YC_6H_4COCl \longrightarrow XC_6H_4CONHNHCOC_6H_4Y$

X	Y	Yield (%)	M.p. (°)	Recrystallising solvent
H	*o*-NO_2	57	214—216 (lit. [14] 212—213)	EtOH
m-NO_2	H	40	220—222 (lit. [15] 216)	EtOH–AcOH
p-NO_2	H	67	234—235 (lit. [16] 236)	AcOH
m-NO_2	*o*-NO_2	48	236—238 *	EtOH–AcOH
p-NO_2	*o*-NO_2	63	280—282 †	AcOH
p-NO_2	*m*-NO_2	44	251—252 (lit. [11] 250—251)	AcOH

* Found: C, 50.6; H, 2.9; N, 16.7. $C_{14}H_{10}N_4O_6$ requires C, 50.9; H, 3.05; N, 17.0%. † Found: C, 50.7; H, 2.9; N, 17.0. $C_{14}H_{10}N_4O_6$ requires C, 50.9; H, 3.05; N, 17.0%.

benzoylhydrazine, similarly obtained, had m.p. 150—152° (lit.,[12] 152°; yield 86%).]

General Procedure.—A solution of the aroyl chloride (11 mmol) in warm xylene (2 ml) was added dropwise to a stirred mixture of the monoaroylhydrazine (11 mmol), anhydrous sodium carbonate (1.17 g, 11 mmol), and dimethylformamide (8 ml). External cooling with ice was used to keep the mixture below 100°. After 2 h, water (30 ml) was added, the mixture was made slightly acidic (5M-HCl), and the product was filtered off and washed with hot water. The compounds thus prepared are listed in Table 6.

2,5-Diaryl-1,3,4-oxadiazoles.—The following procedure is typical. 1,2-Dibenzoylhydrazine (20 g), thionyl chloride (150 ml), and pyridine (0.5 ml) were heated together under reflux for 1 h. The thionyl chloride was then removed by distillation and the residue was recrystallised from an appropriate solvent. Compounds prepared by this route are shown in Table 7.

Nitration of 2,5-Diaryl-1,3,4-oxadiazoles.—The following procedures are taken to be typical.

(a) *With nitric acid alone.* 2,5-Diphenyl-1,3,4-oxadiazole (2.0 g, 9 mmol) was added, with stirring, to fuming nitric acid (*d* 1.5, 25 ml) at 0°. The addition caused the internal temperature to rise to *ca.* 20°. After 2 h stirring at 0° the mixture was poured onto crushed ice, and the product filtered off, washed with saturated sodium hydrogen carbonate (until neutral) and then with water, and finally dried in air at 100°. The yield of dinitro-compounds was essentially quantitative (2.8 g).

For the semi-kinetic study (see Figure 2), portions (2 ml) of the mixture were withdrawn at selected intervals, and worked-up as described above.

(b) *With nitric and sulphuric acids.* To a solution of 2,5-diphenyl-1,3,4-oxadiazole (2.0 g) in concentrated sulphuric acid (5 ml) at 0°, fuming nitric acid (*d* 1.5; 1.8 ml) was added, and the mixture was stirred for 3 h at 0°. It was then poured onto crushed ice and worked up as in (a). Again the yield was essentially quantitative.

(c) *With nitronium tetrafluoroborate.* 2,5-Diphenyl-1,3,4-oxadiazole (1.0 g) was added slowly to a stirred suspension of nitronium tetrafluoroborate (3.0 g) in dry, redistilled sulpholan (10 ml) at 30°. The mixture was then stirred for 2 h at 100°, then cooled and poured into water. The product was filtered off and worked up as in (a). The yield was almost quantitative (98%).

In each case the total product was dissolved in dry, redistilled dioxan, and was analysed by h.p.l.c.

Product Analysis by H.p.l.c.—The chromatograph used was a Pye-Unicam LC3 system with a u.v. spectrophotometric detector set at 254 nm. The column (250 mm × 4.6 mm i.d.) was packed with 10 μm Partisil silica (Reeve Angel): the solvent was a mixture of dry redistilled dioxan and hexane (15 : 85 v/v), and the flow rate was *ca.* 2 ml min^{-1}. Samples (1 μl) were injected by syringe directly on to the column. Peak areas were measured using a fixed arm planimeter: the average of 20 measurements was taken for each area. Each sample was chromatographed four times to check for reproducibility, and the mean values recorded: the deviation in each case was well within 5%.

TABLE 7

2,5-Diaryl-1,3,4-oxadiazoles

Compound	Yield (%)	M.p. (°)	Recrystallisation solvent	$\lambda_{max.}$/nm (log $\varepsilon_{max.}$)	H.p.l.c. 'response factor' (at 254 nm)
(1)	78	135—137 (lit.,[17] 138)	Petroleum (b.p. 60—80°)	282 (4.40)	0.27
(2)	72	119—121 (lit.,[18] 121—122)	EtOH–H_2O	258 (4.15)	0.85
(3)	69	151—152 (lit.,[15] 147)	EtOH	276 (4.40)	0.43
(4)	73	205—206 (lit.,[18] 206.5—208)	Me_2CO	312 (4.41)	0.46
(5)	59	192—194 (lit.,[19] 195)	EtOH–AcOH	252 (4.22)	0.61
(6)	51	166—168 †	EtOH–AcOH	256 (4.34)	0.90
(7)	69	220—222 (lit.,[18] 224—225)	EtOH–AcOH	294 (4.30)	0.40
(8)	58	225—227 (lit.,[20] 228—229)	AcOH	267 (4.49)	1.00
(9)	44	248—249 (lit.,[11] 251.5—252)	AcOH	251 (4.26) 306 (4.41)	0.66
(10)	70	310—312 (lit.,[11] 314.5—315)	Dioxan	317 (4.45)	0.23

† Found: C, 53.6; H, 2.5; N, 18.0. $C_{14}H_8N_4O_5$ requires C, 53.85; H, 2.6; N, 17.9%.

The chromatograph was calibrated using two different standard mixtures of the six 2,5-bisnitrophenyl-1,3,4-oxadiazoles (5)—(10), prepared from the pure compounds in dry dioxan. For each sample, the relative peak areas were divided by the relative concentrations of the components to give 'response factors'. These are shown in

Table 7: compound (8), which has the highest molar extinction coefficient at 254 nm, was arbitrarily assigned a ' response factor ' of 1, and the other values in the Table are related to this arbitrary value.

Chromatography of the nitration product mixtures gave peak areas which were divided by the appropriate 'response factors ' to give the isomer ratios.

We thank Dr. J. T. Sharp, University of Edinburgh, for advice, and Dr. J. R. Clarke and Mr. D. Nichol, I.C.I. Fibres, for technical assistance in regard to the h.p.l.c. analyses. We also thank the S.R.C. and I.C.I. Fibres for the award of a CASE studentship to A.J.G.S.

[9/1270 *Received*, 9*th August*, 1979]

REFERENCES

[1] Houben–Weyl, ' Methoden der Organischen Chemie,' Georg Thieme Verlag, Stuttgart, 1971, 4th edn., Part 10/1, pp. 706—755.

[2] K. Schofield, M. R. Grimmett, and B. R. T. Keene, ' The Azoles,' Cambridge University Press, Cambridge, 1976, pp. 287—291.

[3] A. R. Katritzky and M. Kingsland, *J. Chem. Soc.* (*B*), 1968, 862.

[5] F. De Sarlo and J. H. Ridd, *J. Chem. Soc.* (*B*), 1971, 712.

[5] A. P. Grekov and R. S. Azen, *J. Gen. Chem. U.S.S.R.*, 1961, **31**, 1796.

[6] V. N. Sokolenko, S. P. Suchilina, and R. V. Drupp, *Vopr. Khim. Khim. Tekhnol.*, 1975, **38**, 131 (*Chem. Abs.*, 1976, **84**, 134931).

[7] A. Albert and E. P. Serjeant, ' The Determination of Ionisation Constants,' Chapman and Hall. London, 1971, 2nd edn., p. 44.

[8] A. R. Katritzky, M. Konya, H. O. Tarhan, and A. G. Burton, *J.C.S. Perkin II*, 1975, 1627.

[9] B. M. Lynch and L. Poon, *Canad. J. Chem.*, 1967, **45**, 1431.

[10] H. H. Hatt, *Org. Synth.*, 1943, Coll. Vol. 2, 208.

[11] L. W. Frost, G. M. Bower, J. H. Freeman, H. A. Burgman, E. J. Traynor, and C. R. Ruffing, *J. Polymer Sci.* A–1, 1968, **6**, 215.

[12] T. Curtius and O. Trachmann, *J. prakt. Chem.*, 1895, **51**, 165.

[13] A. T. Dann and W. Davies, *J. Chem. Soc.*, 1929, 1050.

[14] T. Kametani, K. Sota, and M. Shio, *J. Heterocyclic Chem.*, 1970, **7**, 815.

[15] A. P. Grekov and O. P. Shvaika, *J. Gen. Chem. U.S.S.R.*, 1960, **30**, 3763.

[16] R. Stollé and K. O. Leverkus, *Ber.*, 1913, **46**, 4076.

[17] R. Stollé, *J. prakt. Chem.*, 1904, **69**, 145.

[18] R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Chem. Ber.*, 1960, **93**, 2106.

[19] R. Stollé and A. Weindel, *J. prakt. Chem.*, 1906, **74**, 1.

[20] C. C. Walker and H. Shechter, *J. Amer. Chem. Soc.*, 1968, **90**, 5626.