580. *The* ortho : para-*Ratio in Aromatic Substitution. Part I. The Nitration of Methyl Phenethyl Ether.*

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Methyl phenethyl ether, like anisole and acetanilide, has been found to give a far higher proportion of the *o*-nitro-derivative when nitrated with acetyl nitrate than when nitric acid or mixed acid is the reagent. Evidence has been obtained that acetyl nitrate, and other acyl nitrates, do not themselves bring about nitration of the aromatic compound but give rise to dinitrogen pentoxide. This then reacts in two ways: by heterolysis to the nitronium ion, which brings about nitration at the *ortho-*, *meta-*, and *para-*positions in the same proportions as nitric acid; and by reaction at the oxygen atom of methyl phenethyl ether to form an oxonium ion which rearranges, through a six-membered cyclic transition state, to the *o*-nitro-derivative.

Although the factors which govern rates of aromatic substitution at the *meta-* and *para-*positions of monosubstituted benzenes are relatively well understood,[1,2] little is known about the factors which determine the *ortho* : *para*-ratio in these reactions. This is because it is difficult to estimate quantitatively the effect of steric hindrance to substitution at the *ortho*-position. That steric hindrance is important has been established in certain cases (*e.g.*, in the nitration of t-butylbenzene [3]), but the *ortho* : *para*-ratio is often greater than the statistical value of 2 : 1, indicating that any steric hindrance is outweighed by some more powerful effect. In this paper we report the first results of a study of the factors which determine the *ortho* : *para*-ratio in substitution when this ratio is greater than the statistical value.[4]

It is well known that anisole and acetanilide give rise to higher proportions of *o*-nitro-derivative when nitrated with acetyl nitrate than when nitric acid or mixed acid is the reagent.[5-7] Various tentative explanations of this have been advanced, but none is satisfactory. It has been suggested that the change in orientation may be due to a change in the nitrating species,[8] but this seems unlikely because toluene forms *o*- and *p*-nitro-derivatives in the same proportions with acetyl nitrate as with nitric acid,[6] which indicates that the species responsible for nitration is the same in each case. This follows from the fact that different reagents would almost certainly have different selectivities.[9] Paul has attributed the change in orientation to an electrostatic effect.[10] In anisole, the dipole of the aromatic C–O bond has its negative end towards carbon, resulting in the *ortho*-position's being negatively polarised with respect to the *para*-position, while in chlorobenzene and bromobenzene the corresponding dipole is towards the halogen atom, the *ortho-* being more positively polarised than the *para*-position. This produces an electrostatic attraction between the reagent and the *ortho*-carbon in anisole, aiding *ortho*-substitution, and a repulsion in the halogenobenzenes, retarding *ortho*-substitution. In solvents of low dielectric constant this electrostatic influence is relatively more important, and results in the observed change in orientation. However, the isomer ratios obtained by Paul for the nitration of chlorobenzene and bromobenzene are at variance with the values obtained

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[1] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953.
[2] de la Mare and Ridd, " Aromatic Substitution," Butterworths Scientific Publ., London, 1959.
[3] Nelson and Brown, *J. Amer. Chem. Soc.*, 1951, **73**, 5605.
[4] Norman and Radda, *Proc. Chem. Soc.*, 1960, 423.
[5] Griffiths, Walkey, and Watson, *J.*, 1934, 631.
[6] Halvarson and Melander, *Arkiv Kemi*, 1957, **11**, 77.
[7] Holleman, *Chem. Rev.*, 1925, 1 187; Arnall and Lewis, *J. Soc. Chem. Ind.*, 1929, **48**, 159T.
[8] Ref. 2, p. 76.
[9] Nelson, *J. Org. Chem.*, 1956, **21**, 145.
[10] Paul, *J. Amer. Chem. Soc.*, 1958, **80**, 5332.

by other workers.[11,12] Moreover, Paul's view that the electrostatic effect is enhanced in solvents of low dielectric constant is contraverted by the fact that the nitration of anisole in acetic acid,[5] which has a lower dielectric constant than acetic anhydride (the usual solvent for reactions with acetyl nitrate), gives the same isomer distribution as nitric acid. Halvarson and Melander [6] suggested that the high *ortho* : *para*-ratio in the nitration with acetyl nitrate might be due to initial attack of the nitrating species at oxygen, followed by an intramolecular rearrangement to the *o*-nitro-compound. They viewed this as an attractive but unlikely explanation.

Two problems arise from these data: first, to discover the nature of the nitrating species in solutions of acetyl nitrate; and secondly, to find whether the observed high *ortho* : *para*-ratios result from the presence in the molecule of an atom with an unshared pair of electrons bonded to the benzene nucleus. We chose to examine the nitration of methyl phenethyl ether, $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}OMe$, since this compound contains an oxygen atom not bonded to the benzene ring. It is also more suitable than anisole in that its reactivity in nitration is not likely to be complicated by nitrosation, and that cleavage of the CH_3–O bond is not so easy in an aliphatic as in an aromatic ether.

None of the three nitro-derivatives of methyl phenethyl ether has previously been reported. The *p*-nitro-compound was readily prepared from *p*-nitrophenethyl bromide, but attempts to make the *o*- and the *m*-nitro-isomer through the corresponding nitrophenylacetaldehydes were unsuccessful because Darzens condensations with the nitrobenzaldehyes gave glycidic acids that formed polymers under the conditions necessary for decarboxylation. The nitrophenethyl alcohols were prepared by reduction of the corresponding acids with sodium borohydride in the presence of aluminium trichloride (a method specific for the reduction of CO_2H to $CH_2{\cdot}OH$ in the presence of nitro-groups [13]) and were converted into the methyl ethers with diazomethane.[14]

Methyl phenethyl ether was nitrated with nitric acid alone, with mixed acid, with nitric acid in acetic anhydride (the system most commonly used for studying the reactions of acetyl nitrate), and with acetyl nitrate in acetonitrile. The temperature of reaction was constant within ±0·5°, and in all reactions less than one equivalent of nitrating agent was used in order to minimise dinitration. The mixtures of nitro-derivatives were analysed by gas chromatography, complete resolution of the three isomers being obtained. Isomer distributions are set out in Table 1.

TABLE 1. *Nitration of methyl phenethyl ether.*

		Orientation (%)		
Nitrating agent	Temp.	*ortho*	*meta*	*para*
Nitric–sulphuric acid	0°	28·9	8·7	62·4
	25	31·6	9·4	59·0
Nitric acid	25	40·2	6·6	53·2
Nitric acid in nitromethane	25	41·2	3·0	55·8
Nitric acid in acetic anhydride	0	64·4	3·6	32·0
	25	62·3	3·7	34·0
Acetyl nitrate in acetonitrile	0	66·0	4·2	29·8

We found that, as occurred with anisole and acetanilide, the *ortho* : *para*-ratio is considerably higher in nitrations by acetyl nitrate. The *meta* : *para*-ratios, however, are essentially the same for nitration with nitric acid and with acetyl nitrate. If the change in orientation were the result of protonation of the oxygen atom in the aromatic compound by nitric acid, not only would the *ortho* : *para*-ratio be lower in the acid conditions, but the *meta* : *para*-ratio should be higher, for such protonation would result in greater deactivation of the *para*- than of the *meta*-position. This is not the case, although the slightly greater

[11] Roberts, Sanford, Sixma, Cerfontain, and Zagt, *J. Amer. Chem. Soc.*, 1954, **76**, 4525.
[12] Bird and Ingold, *J.*, 1938, 918.
[13] Brown and Subba Rao, *J. Amer. Chem. Soc.*, 1956, **78**, 2582.
[14] Müller and Rundel, *Angew. Chem.*, 1958, **70**, 105.

proportion of *m*-nitro-derivative with mixed acid is compatible with a small degree of protonation. Nor can the change be due to the fact that nitration with nitric acid takes place in a two-phase system while that with acetyl nitrate takes place in homogeneous conditions, for nitration with nitric acid in nitromethane solution gives essentially the same *ortho* : *para*-ratio as nitric acid alone. Because the degree of nitration by nitric acid in nitromethane was extremely small, even after very long reaction times, the results under these conditions are not considered as accurate as the remainder.

Thus the variation in *ortho* : *para*-ratios results not simply from a diminished reactivity of the *ortho*-position in acid solutions. (Further evidence for this conclusion is adduced later.)

That toluene gives *o*- and *p*-nitro-derivatives in the same proportions with acetyl nitrate as with nitric acid[6] is evidence that there is a nitrating species common to both systems. This must be the nitronium ion, which is known to be responsible for nitration with nitric acid. Yet if the nitronium ion alone were responsible for nitration of the ether with acetyl nitrate, the isomer ratio should be the same as that for nitration with nitric acid. There must therefore be another nitrating species present in acetyl nitrate which is capable of nitrating only the *ortho*-position of the ether, and not either the *para*-position of the ether or the *ortho*- or *para*-position of toluene. This conclusion is supported by a comparison of the partial rate factors for the nitration by acetyl nitrate of methyl phenethyl ether with those of ethylbenzene.[15] The former compound is very much less reactive than the latter in the *para*-position, consistently with the electron-withdrawing nature of the methoxyl group, but the two hardly differ in reactivity at their *ortho*-positions, suggesting that an additional mode of nitration at the *ortho*-position of the ether approximately counterbalances the loss in reactivity expected to result from substitution of methoxyl for hydrogen.

TABLE 2. *Rate factors for nitration.*

Compound	*ortho*	*meta*	*para*
$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}OMe$	25·9	1·5	25·8
$Ph{\cdot}CH_2{\cdot}CH_3$	31·4	2·3	69·5

Nitration of methyl phenethyl ether with benzoyl nitrate and with *p*-nitrobenzoyl nitrate in acetonitrile solution gives nitro-derivatives in the same proportions as when acetyl nitrate is the reagent ($BzNO_3$ and $NO_2{\cdot}C_6H_4{\cdot}CO{\cdot}NO_3$ respectively: *ortho* 65·7, 64·9; *meta* 3·6, 4·7; *para* 30·7, 30·4%). We conclude from this that the species which is responsible for the enhanced *ortho*-reactivity is common to these three acyl nitrates. The only nitrating species (other than NO_2^+) known to be present in such systems is dinitrogen pentoxide.[16] There is evidence that the nitration by benzoyl nitrate of comparatively unreactive aromatic compounds (such as chlorobenzene) involves dinitrogen pentoxide as the active species,[17] although Paul found that the kinetics of the nitration of benzene with nitric acid in acetic anhydride were compatible with attack by the nitronium ion but not with attack by dinitrogen pentoxide.[18] That dinitrogen pentoxide is the reagent responsible for the high proportion of *ortho*-substitution in the present case is supported by our finding that dinitrogen pentoxide itself gives rise to the same isomer distribution as the acyl nitrates (see Table 3). Further, toluene gives the same isomer distribution with dinitrogen pentoxide as with acetyl nitrate.

Our results, together with the other evidence which we have discussed, are compatible with the following mechanism for the enhanced reactivity of the *ortho*-position of methyl phenethyl ether in its reaction with acyl nitrates. The acyl nitrate, itself not reactive

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[15] Knowles, Norman, and Radda, *J.*, 1960, 4885.

[16] Chèdin and Fénéant, *Compt. rend.*, 1949, **229**, 115; Malkova, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **24**, 1151; Vandoni and Viala, *Mem. Services chim. État*, 1945, **32**, 80.

[17] Gold, Hughes, and Ingold, *J.*, 1950, 2467.

[18] Paul, *J. Amer. Chem. Soc.*, 1958, **80**, 5329.

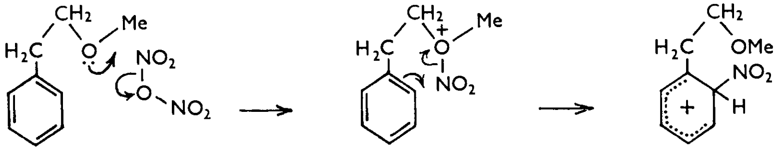
enough to bring about nitration of the aromatic compound, gives rise to dinitrogen pentoxide (and acyl anhydride) which reacts in two ways. It undergoes slow heterolysis to the nitronium ion which reacts with the aromatic compound to give *o*-, *m*-, and *p*-nitro-derivatives in the same proportions as when nitric acid is the reagent; and at the same time there is an additional mode of nitration at the *ortho*-position, dependent on the presence of the oxygen atom of the ether, and brought about by dinitrogen pentoxide itself.

TABLE 3. *Orientation (%) of nitration by dinitrogen pentoxide in acetonitrile at* 0°.

Compound	*ortho*	*meta*	*para*
Methyl phenethyl ether	68·8	3·3	27·9
Toluene	59·8	3·3	36·9

It is possible that nitronium ion might be generated directly from the acyl nitrate by heterolysis of the O–N bond. If this were to happen, it is unlikely that each of three acyl nitrates should generate nitronium ion and dinitrogen pentoxide at the same relative rates, as is required by the finding that the isomer distribution is constant for these three reagents. This route to nitronium ion can probably be excluded.

The rôle of the oxygen atom of methyl phenethyl ether has now to be explained. We consider that nitration by dinitrogen pentoxide involves an S_N2-type displacement (as shown) in which the oxygen atom displaces nitrate ion from covalent dinitrogen pentoxide, giving a charged intermediate. This rearranges through a six-membered cyclic transition state to the usual σ-bonded intermediate of aromatic nitration and thence to the *o*-nitro-derivative. This provides a route for the formation of the *o*-nitro-derivative which is available neither at the *para*-position of the ether, nor at the *ortho*-positions of ethylbenzene or toluene. It is reasonable that the displacement occurs on dinitrogen pentoxide rather than on the acyl nitrate as our observations require, because the nitrate ion has greater stability than a carboxylate ion and should therefore be a better leaving group in such displacements. It is known also that the *O*-nitration of alcohols by acetyl nitrate involves dinitrogen pentoxide as the attacking entity.[19]



The following evidence supports the cyclic mechanism proposed above:

(i) Addition of a catalytic amount of sulphuric acid in the nitration of methyl phenethyl ether with acetyl nitrate decreases the proportion of *o*-nitro-derivative from 62·3 to 55·1%, while the *meta* : *para*-ratio remains effectively constant. The orientation, at 25°, is: $o : m : p = 55{\cdot}1 : 5{\cdot}0 : 39{\cdot}9$. The constancy of the *meta* : *para*-ratio argues against prescription of the fall in the proportion of *ortho*-isomer to protonation of the ether. On the other hand, there is evidence that both nitric and sulphuric acid bring about the dissociation of dinitrogen pentoxide into nitronium ions, the kinetic results for the reaction with nitric acid having been interpreted on the basis that the acid molecules aggregate around the pentoxide causing ionic dissociation:[20] $NO_2{\cdot}O{\cdot}NO_2 + (x + y)HNO_3 \rightleftharpoons NO_2^+(xHNO_3) + NO_3^-(yHNO_3)$. This increases the rate of " normal " nitration relatively to that which occurs by displacement on dinitrogen pentoxide.

(ii) The operation of a mechanism similar to that proposed for methyl phenethyl ether in the case of methyl 3-phenylpropyl ether would involve the formation of a seven-membered cyclic transition state which should be less readily formed than its six-membered analogue. We found that the nitro-derivatives of methyl 3-phenylpropyl ether are

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[19] Bonner, *J.*, 1959, 3908.

[20] Gold, Hughes, Ingold, and Williams, *J.*, 1950, 2452.

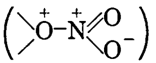
formed (at 0°) in essentially the same proportions when nitric acid (*o* 44·2, *m* 3·8, *p* 52·0%) or acetyl nitrate (*o* 43·0, *m* 4·0, *p* 53·0%) is the reagent.

(iii) Benzyl methyl ether gives rise to a higher proportion of its *o*-nitro-derivative with acetyl nitrate than with nitric acid (see Table 4). A mechanism analogous to that proposed for nitration of methyl phenethyl ether would involve formation of a five-membered cyclic transition state, which should be easy. (The first two results in Table 4 are not as accurately established as those for nitration of methyl phenethyl ether because the extent of nitration was kept extremely small in order to avoid side-reactions.)

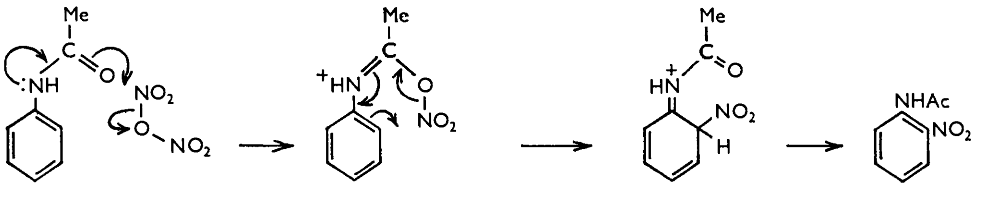
TABLE 4. *Orientation (%) of nitration of benzyl methyl ether at* 25°.

Nitrating agent	*ortho*	*meta*	*para*
Nitric acid	38·5	12·8	48·7
Nitric acid–sulphuric acid [21]	28·6	18·1	53·3
Nitric acid in acetic anhydride [21]	51·3	6·8	41·9

Finally, comparison of the partial rate factors for the nitration by acetyl nitrate of methyl phenethyl ether with those of methyl 3-phenylpropyl ether (*o* 14·6, *m* 1·2, *p* 34·3) further supports the conclusion that the variation in the *ortho* : *para*-ratios does not result from diminished reactivity of the *ortho*-position in acid solutions. The greater reactivity of the *para*-position in the 3-phenylpropyl ether than in the phenethyl ether results from the greater distance of the methoxyl group from the aromatic ring in the former compound. The greater reactivity of the *ortho*-position in the phenethyl ether than in the phenylpropyl ether indicates that there is an enhancement of the reactivity of the *ortho*-position in the first compound.

In summary, all the facts are satisfactorily correlated by the proposal that, in acyl nitrate systems, methyl phenethyl ether is nitrated at the *ortho*-position not only by the nitronium ion but also by the sterically favourable rearrangement of an oxonium ion formed by reaction of dinitrogen pentoxide with the oxygen of the ether. That this intermediate oxonium ion has two atoms bonded together each of which is positively charged  $\left(>\overset{+}{\mathrm{O}}-\overset{+}{\mathrm{N}}{<}^{\mathrm{O}}_{\mathrm{O}^-}\right)$ is compatible with the existence of the ion as an intermediate, for it resembles that involved in the nitramine rearrangement.[22] The mechanism also has certain features in common with that accepted for the Claisen rearrangement; [23] and it is notable that methyl phenethyl sulphide gives an unusually high proportion of *ortho*-derivative in a Friedel–Crafts reaction.[24]

It is tempting to extend the mechanism proposed above to include the reactions of anisole and acetanilide. Thus, the mechanism for the increased *ortho*-reactivity in the nitration of acetanilide with acetyl nitrate would be as follows:



We have found that anisole gives the same proportions of nitro-derivatives with dinitrogen pentoxide (at 0°: *o* 70·9, *m* 0, *p* 29·1%) as with acetyl nitrate (*o* 70·0, *m* 0, *p* 30·0%), which accords with Halvarson and Melander's proposal [6] that in this reaction the oxygen atom of anisole may react with dinitrogen pentoxide to form an intermediate which rearranges to the *o*-nitro-derivative. We consider that this process may be represented analogously,

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[21] Knowles and Norman, *J.*, 1961, 2938.

[22] Brownstein, Bunton, and Hughes, *J.*, 1958, 4354.

[23] Ref. 1, p. 598.

[24] Saunders and Edison, *J. Amer. Chem. Soc.*, 1960, **82**, 138.

though confirmation of such reaction paths for anisole and acetanilide awaits further experimentation.

EXPERIMENTAL

Materials.—Fuming nitric acid (B.D.H. " AnalaR; " *d* 1·5) was used in all quantitative nitrations. Acetic anhydride, acetyl chloride, benzoyl chloride, *p*-nitrobenzoyl chloride, acetonitrile, nitromethane, toluene, anisole, and benzyl methyl ether were commercial materials purified by distillation. Methyl phenethyl ether was prepared by Gupta, Lal, and Shukla's method [25] and purified by three fractional distillations, the final product being collected at 192—193°. Methyl 3-phenylpropyl ether was prepared similarly, from 3-phenylpropan-1-ol (101 g.), dimethyl sulphate (70 ml.), and sodium hydroxide (59 g.). The product was purified by fractional distillation, the fraction boiling at 213° (66 g., 59%) being collected.

Syntheses of Reference Compounds.—The nitro-derivatives of anisole were commercial materials which were purified by recrystallisation or distillation, their purities being checked by gas chromatography. The nitro-derivatives of toluene and benzyl methyl ether were available.[15, 21]

Methyl 4-*nitrophenethyl ether.* 4-Nitrophenethyl bromide [26] (5·1 g.) in hot methanol (10 ml.) was added to a solution of sodium (1·5 g.) in methanol (10 ml.), and the mixture was refluxed for 2 hr. After cooling, water was added and organic material was extracted with ether and washed with water. Evaporation gave pale yellow *methyl* 4-*nitrophenethyl ether*, m. p. 62·5—63° (from light petroleum) (Found: C, 59·7; H, 6·6; N, 7·6. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%).

Methyl 2-*nitrophenethyl ether.* *o*-Nitrophenylacetic acid [27] (6 g., 0·03 mole) and sodium borohydride (3 g., 0·09 mole) were dissolved in diethylene glycol dimethyl ether (dried over lithium hydride and distilled under reduced pressure) (62 ml.). Aluminium trichloride (purified by sublimation) (1 g.) in diethylene glycol dimethyl ether (8 ml.) was slowly added to this solution. The mixture was kept at 50—60° for 3 hr. After decomposition of the excess of sodium borohydride with ice and dilute hydrochloric acid, the ether extract was dried (Na_2SO_4) and the solvents were removed. Distillation yielded 2-nitrophenethyl alcohol, b. p. 133°/0·3 mm. (lit.,[28] 155°/1 mm.) (5·1 g., 92%). This reduction when carried out on a larger quantity of the acid (22 g.) gave only a 60% yield. Diazomethane, from " Diazald " (21·9 g.), was distilled, with ether, into an ice-cooled solution of 2-nitrophenethyl alcohol (5·9 g.) and the boron trifluoride–ether complex (0·6 g.) in dry ether. After 3 hr. at room temperature the solution was washed with water. *Methyl* 2-*nitrophenethyl ether* was purified by chromatography on alumina in light petroleum–benzene (1 : 1 v/v) to give a pale yellow liquid, n^{25} 1·5274 (2·3 g., 36%) (Found: C, 60·7; H, 6·3; N, 7·8%).

Methyl 3-*nitrophenethyl ether.* *m*-Nitrophenylacetic acid [29] (18 g.) was reduced as described for the *o*-nitro-compound, and gave yellow needles of 3-*nitrophenethyl alcohol* (11 g., 69%), m. p. 48·5—49·5° (from light petroleum–benzene) (Found: C, 57·4; H, 5·4; N, 8·6. $C_8H_9NO_3$ requires C, 57·5; H, 5·4; N, 8·4%). The alcohol was methylated as described for the *o*-nitro-compound, giving the *ether* (30%), m. p. 28—28·5° (from light petroleum–benzene) (Found: C, 59·5; H, 6·2; N, 7·8%).

Nitro-derivatives of methyl 3-*phenylpropyl ether.* These compounds were not characterised separately. When log (retention time) was plotted against the number of carbon atoms in the mononitro-derivatives of benzyl methyl ether, methyl phenethyl ether, and methyl 3-phenylpropyl ether (the nitro-derivatives of the last compound being obtained as a mixture by direct nitration), three straight lines were obtained. Each passed through three points, two of which corresponded to nitro-derivatives of the first two compounds having the same orientation, while the third corresponded to one nitro-derivative of methyl 3-phenylpropyl ether. Since the logarithm of the retention time of each member of a homologous series, measured under the same conditions, is proportional to the number of carbon atoms in the chain,[30] it was concluded

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[25] Gupta, Lal, and Shukla, *J. Proc. Inst. Chemists* (*India*), 1956, **28**, 39. (*Chem. Abs.*, 1956, **50**, 14,178.)

[26] Foreman and McElvain, *J. Amer. Chem. Soc.*, 1940, **62**, 1435.

[27] Reissert, *Ber.*, 1897, **30**, 1041; 1908, **41**, 3814, 3925.

[28] Sebastien, Sabetay, and Blèger, *Bull. Soc. chim. France*, 1931, **49**, 3.

[29] Gabriel and Borgman, *Ber.*, 1883, **16**, 2064.

[30] Ray, *J. Appl. Chem.*, 1954, **4**, 21; James and Martin, *Biochem. J.*, 1952, **50**, 679.

that the order of retention times of the nitro-derivatives of methyl 3-phenylpropyl ether was *o*- < *m*- < *p*- (see Table 5).

TABLE 5. *Retention times of nitro-derivatives.*

Compound	Retention times of derivatives (min.) 2-Nitro	3-Nitro	4-Nitro
Benzyl methyl ether	26·8	34·8	39·0
Methyl phenethyl ether	40·0	55·0	62·0
Methyl 3-phenylpropyl ether	57·0	80·0	94·0

Nitrations.—Reactions were carried out at 0° and 25°, the nitrating mixture (0·005 mole) being added to the aromatic compound (0·01 mole) during 1 hr. with shaking. The temperature variation was not more than 0·5°. Individual nitration mixtures and reaction times were as follows:

Nitric acid in acetic anhydride. A solution of nitric acid (0·005 mole) in acetic anhydride (0·005 mole) was made up at 0°. Nitration of the aromatic compound was stopped after 2 hr. by addition of water.

Nitric–sulphuric acid. A 1 : 1 (v/v) mixture of the two acids was used. Reaction with the aromatic compound was continued for 2 hr. after addition of all the nitrating mixture.

Nitric acid. A longer time (5 hr.) was necessary to obtain a sufficient degree of nitration for accurate analysis.

Nitric acid in nitromethane. The aromatic compound (0·01 mole) was dissolved in nitromethane (0·5 ml.), and nitric acid (0·005 mole) was added in the usual manner. The extent of nitration was small even after 40 hr.

Acyl nitrates in acetonitrile. The acyl nitrate was prepared *in situ*.[31] Silver nitrate (0·005 mole) and the aromatic compound (0·01 mole) were dissolved in acetonitrile (1 ml.), and a solution of the acyl chloride (0·005 mole) in acetonitrile (0·4 ml.) was added slowly at the required temperature. Reaction was stopped after 3 hr.

Dinitrogen pentoxide in acetonitrile. Dinitrogen pentoxide [20] (0·005 mole) was dissolved in acetonitrile (0·4 ml.), and the solution was added slowly to the aromatic compound (0·01 mole) in acetonitrile (1 ml.). The reaction time was 3 hr.

Gas Chromatography.—After nitration had been stopped by the addition of water, the reaction mixtures were extracted with ether four times and the ethereal solutions, after being concentrated, were analysed by gas chromatography. The optimum conditions found for analysis of the nitro-derivatives of the aromatic substrates are set out in Table 6. The column was packed with Apiezon " L " grease (20% w/w) coated on Embacel except for the resolution of the nitroanisoles, for which it was packed with 2,4,7-trinitrofluorenone (10% w/w) coated on firebrick.[32] The carrier-gas was nitrogen; a hydrogen-inject flame ionisation detector coupled to a Sunvic recorder gave a linear response.

TABLE 6. *Operating conditions and retention times for analysis of nitro-derivatives.*

Aromatic compound	Column length (cm.)	Flow-rate (ml./min.)	Temp.	Retention times (min.) *o*	*m*	*p*
Methyl phenethyl ether	200	25	175°	36	50	60
Methyl 3-phenylpropyl ether	400	30	185	57	80	94
Benzyl methyl ether	200	30	160	30	43	52
Anisole	200	20	175	60	72	80

In the conditions set out, the three nitro-isomers of each compound were completely resolved. The isomer distributions were calculted by measuring the peak areas as described previously.[15] It was shown by injecting synthetic mixtures that the peak areas were proportional to the amounts of the isomers present. It was also shown, by subjecting synthetic mixtures of isomers to the same extraction procedure as that used for the reaction mixtures, that no preferential loss of any of the isomers occurred. The results reported are in every case the mean values from the analyses of at least two nitrations each of which was analysed at least twice. Some representative analyses are set out in Table 7.

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[31] Burton and Praill, *J.*, 1955, 729.

[32] Norman, *Proc. Chem. Soc.*, 1958, 151.

TABLE 7. *Analysis of some nitration mixtures.*

Compound	Nitrating agent	Temperature	Isomer distribution *ortho*	*meta*	*para*
$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}OMe$	HNO_3	25°	40·1, 40·4, 40·2	7·0, 6·2, 6·8	52·9, 53·7, 52·8
$Ph{\cdot}[CH_2]_3{\cdot}OMe$	HNO_3–Ac_2O	0	44·7, 43·7	4·0, 3·6	51·3, 52·7

The conditions used for analysis of the nitrotoluenes were as those reported previously.[15]

Competitive Nitrations.—The overall reactivities of methyl phenethyl and 3-phenylpropyl ether relatively to that of toluene were determined, for nitration by acetyl nitrate at 0°, by the method reported previously.[15] Decane was used as the internal standard. Using the value of 27 for the reactivity of toluene relative to benzene, measured under the same conditions as ours,[33] enabled the overall reactivities relative to that of benzene to be calculated. These are shown in Table 8.

TABLE 8. *Competitive experiments.*

Compound	Reactivity rel. to toluene	Rel. to C_6H_6
$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}OMe$	0·445, 0·493, 0·585, 0·445, 0·548, 0·445	—
	average 0·493 ± 0·050	13·4 ± 1·3
$Ph{\cdot}[CH_2]_3{\cdot}OMe$	0·378, 0·441, 0·374, 0·434, 0·378	—
	average 0·401 ± 0·029	10·8 ± 0·8

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[33] Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959.