

220. Nitration of Durene and Pentamethylbenzene with Nitronium Salts in Nitromethane and Acetonitrile

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Summary. Nature and proportions of the products formed in the nitrations mentioned in the title are affected by the process of mixing.

Pentamethylnitrobenzene, formed initially in the nitration of pentamethylbenzene, is attacked by a nitronium ion at a position *meta* to the nitro-group. In the σ -complex formed, loss of a proton from a methyl group leads to production of by-products and release of nitrite ions. The nitrous acid formed is protonated, and water is displaced from the nitrous acidium ion by the anion, PF_6^- , giving the nitrosonium ion which forms a 1:1 symmetric molecular complex with pentamethylbenzene. A similar complex is formed in the reaction between durene and nitronium salts.

The results are consistent with the view that no σ -bond is formed between the aromatic compound and the nitrosonium ion.

1. Introduction. – The nitration of aromatic hydrocarbons with nitronium salts in aprotic solvents, principally tetramethylene sulfone (sulfolane) and nitromethane, has been extensively investigated by *Olah et al.* (for a summary see [1]; for a critical review see [2]). These workers used the method of competitive nitration to determine the rates of nitration, relative to that of benzene, of a number of aromatic hydrocarbons. The relative rates were smaller ($k_{\text{toluene}}:k_{\text{benzene}} = \text{ca. } 1.5$) than those obtained from nitration with nitric acid ($k_{\text{toluene}}:k_{\text{benzene}} = \text{ca. } 20$), but the orientation of nitration was very similar.

The experimental conditions employed by *Olah et al.* have been criticised. The low substrate selectivity observed by them was thought by some workers to be a direct consequence of incomplete mixing of the reagents. *Tolygesi* [3] observed that using very efficient mixing systems and low concentrations of reactants a more "normal" substrate selectivity was obtained. However, *Olah & Overchuk* [4] suggested that impurities such as water and dihydrothiophene-1,1-dioxide were present in the solvent used by *Tolygesi* and that these impurities would react with the nitronium salt to form other nitrating agents.

Incomplete mixing of the reagents occurs in the nitration of dibenzyl with nitronium tetrafluoroborate in sulfolane. *Ridd et al.* [5] observed that a high percentage of dinitrobenzyls was formed even when dibenzyl was present in five-fold excess. It was possible to calculate that the nitronium ions were effectively mixed with about 1.2 times the equivalent number of aromatic rings before nitration is complete. The observation that dibenzyl undergoes substantial dinitration in nitrations with nitric acid [6] would appear to cast some doubt upon the conclusions reached by *Ridd et al.*; but under conditions where mixing is unimportant the amount of disubstitution is small [7]. From these results it is easy to understand why low substrate selectivities were observed under the conditions employed by *Olah et al.*

Work in this laboratory has been concerned with the nitration of pentamethylbenzene [8] and durene [9] with nitronium salts in aprotic solvents. In the case of durene, the evidence found suggests that nitration is controlled by mixing. Thus, the product ratio dinitrodurene/mononitrodurene decreases with diminishing initial

concentrations of the reactants and with a faster mixing. Nitration of pentamethylbenzene has been suggested to proceed *via* a rapidly formed adduct which decomposes in a slow reaction to yield 15–30% pentamethylnitrobenzene and unidentified by-products.

The nitration of both of these alkylbenzenes is complicated by formation of coloured complexes. The aim of the present work was to determine their nature and their effect, if any, on the nitration.

2. Preliminary Investigation of the Complexes formed in the Nitration of Durene and Pentamethylbenzene with Nitronium Salts in Nitromethane and Acetonitrile. – 2.1. *Role of the Complexes in Nitration.* When solutions of the aromatic compounds and nitronium salts in nitromethane or acetonitrile are mixed in a 1:1 ratio, dark red complexes are formed which are stable in the absence of moisture but decompose immediately on the addition of water or ammonia. The UV. spectrum of the complex in acetonitrile has a maximum at 340 nm in the case of pentamethylbenzene and at 335 nm in the case of durene. Solvent absorption precludes an examination of the UV. spectra of the complexes formed in nitromethane.

We first considered the possibility that these complexes were precursors of the nitro-compounds. In this case, the concentration of the complex in the nitration solution should vary according to the initial concentrations of the reactants. We measured the optical densities of the complexes, formed by mixing equal volumes of solutions of durene and nitronium hexafluorophosphate in acetonitrile. The solutions were then quenched with ammonia and the products determined using gas chromatography (results see Table 1).

Table 1. Nitration of durene with nitronium hexafluorophosphate in acetonitrile at 20°

Durene: NO ₂ PF ₆ ^{a)} (1:1 mixed)	O.D. _{335 nm}	Dinitrodurene/ Mononitrodurene ^{d)}
0.01 M	1.12 ^{b)}	0.34
0.02 M	2.19 ^{b)}	0.55
0.10 M	1.25 ^{c)}	1.00

a) Concentration after mixing.
 b) 0.1 cm cell.
 c) 0.01 cm cell.
 d) Total yield of nitro-compounds was ≥ 95%. See [9] for details of the gas chromatographic method.

The proportions of the di- and mononitro-compounds in the final product vary considerably with the initial concentrations of the reactants, but the concentration of the complex does not change very much. Similar observations were made for the nitration of durene in nitromethane, and pentamethylbenzene in nitromethane or acetonitrile. The results indicate that the structures of the complexes and the nitro-compounds are unrelated to each other; it is unlikely that these complexes are formed from the aromatic compounds and the nitronium salt.

In independent experiments we found that the nitro-compounds do not form similar complexes with nitronium salts or with the alkylbenzenes. The possibility

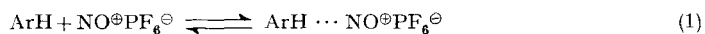
remains that the aromatic compounds form complexes with other species formed as by-products during nitration or with impurities present in the nitronium salt.

Aromatic hydrocarbons are known to form coloured complexes in a number of nitrating systems (for a useful summary see [1]). In most cases the nature of these complexes is in doubt. *Benford & Ingold* [10] observed that benzene and some alkylbenzenes formed coloured complexes with a lower oxide of nitrogen in the presence of an anhydrous condensing agent. The complexes were formed during the nitration of these compounds by nitric acid in nitromethane and acetonitrile, and their production was dependent upon the amount of nitrous acid initially present in the nitric acid. Later [11] it was suggested that the complexes derived from diphenylaminyl oxide. More recent work has shown that several aromatic compounds form coloured complexes of the types $\text{ArH} \cdot \text{NO}^{\oplus}$ and $2\text{ArH} \cdot \text{NO}^{\oplus}$ with the nitrosonium ion in 98% sulfuric acid [12].

Under the conditions of the present experiments, nitrous acid is produced in the reactions leading to the formation of the by-products [9]. Furthermore, our samples of nitronium salts contain from 3–11% of the corresponding nitrosonium salts. Therefore, the complexes observed in this work and the previous work [8] [9] may be formed between the aromatic compounds and the nitrosonium ion. The nature of these complexes is discussed in the next section.

2.2. Complexes formed between Durene, Pentamethylbenzene and Nitrosonium Salts, in Nitromethane and Acetonitrile. On mixing solutions of the aromatic compounds with solutions of nitrosonium salts in nitromethane or acetonitrile, dark red-brown mixtures were obtained which showed UV. absorption maxima at 340 nm in the case of pentamethylbenzene and at 335 nm for durene. For reasons which will be apparent later, the visible spectra (s. Table 2) were examined of complexes prepared using different initial concentrations of reactants.

Application of *Job's* method [13] showed that 1:1 complexes were formed in both solvents. After quenching the solutions with water, the aromatic compound and the nitrosonium ion (determined as nitrous acid) were quantitatively recovered. This strongly suggests that the complexes have no σ -bond between the electrophile and the alkylbenzene. If we assume similar ϵ values for all the complexes formed at a reactant concentration of 0.1 M, then the equilibrium (1) lies further to the left in the



case of mesitylene than in the cases of durene and pentamethylbenzene (see Table 2). This situation parallels that found for molecular complexes [14] *i.e.* the amount of complex present at equilibrium depends on the π - rather than the σ -basicity of the aromatic compounds.

In the IR. spectra of the complexes in nitromethane [$\text{ArH}(0.2\text{M}) : \text{NOPF}_6(0.2\text{M})$, 1:1 mixed] the band at 2260 cm^{-1} , representing the N–O stretching vibration [15] in the nitrosonium salt, is absent. A new, more intense band appears at 1900 cm^{-1} in the pentamethylbenzene complex and at 1930 cm^{-1} in the durene complex. These bands are peculiar to the complexes; they are not found in the IR. spectra of the aromatic compounds or of the final products. In our opinion, these bands represent the N–O stretching vibration of the complexed nitrosonium ion.

Table 2. Visible spectra of the complexes formed between mesitylene, durene, pentamethylbenzene, and nitrosonium hexafluorophosphate^{a)}, in nitromethane and acetonitrile at 20°

Alkylbenzene: NOPF ₆ (0.1 M)		Optical density ^{b)}									
		In acetonitrile				In nitromethane					
		Pentamethylbenzene		Durene		Mesitylene		Pentamethylbenzene		Durene	
(0.1 M)	d)	650 nm	600 nm	650 nm	600 nm	650 nm	600 nm	650 nm	600 nm	650 nm	600 nm
2	:	1	0.300	0.705	0.240	0.601		0.310	0.735	0.282	0.695
1	:	1	0.401	0.960	0.316	0.796	0.122	0.470	1.105	0.428	1.020
1	:	2	0.253	0.599	0.214	0.543		0.314	0.735	0.294	0.703
e)											
0.2 M		0.02 M	0.087	0.197	0.067	0.159					
0.1 M		0.02 M	0.078	0.174	0.075	0.156					
0.02 M		0.02 M	0.065	0.137	0.035	0.085					
0.1 M		0.01 M					0.047	0.099	0.184 ^{e)}	0.422 ^{e)}	
0.01 M		0.01 M					0.029	0.074	0.137 ^{e)}	0.321 ^{e)}	
0.5 M		0.1 M					0.550	1.205	0.519	1.157	

a) Purity 95.1%.

b) 0.1 cm cells used except where stated.

c) 0.5 cm cells.

d) Job's method. Concentration of the solutions before mixing: 0.1 M; solutions mixed in the proportions (v/v) shown.

e) Concentrations before mixing equal volumes of solutions.

a) Purity 95.1%.

b) 0.1 cm cells used except where stated.

c) 0.5 cm cells.

d) Job's method. Concentration of the solutions before mixing: 0.1 M; solutions mixed in the proportions (*v/v*) shown.

e) Concentrations before mixing equal volumes of solutions.

In acetonitrile the situation is a little more complicated. No band at 2260 cm^{-1} is observed in the infrared spectrum of the nitrosonium salt; this band is replaced by a much more intense band at 1850 cm^{-1} . In view of the ability of acetonitrile to form complexes with cations such as $\text{Ag}^{\oplus}$ (see *e.g.* [16]) and $\text{NO}_2^{\oplus}$ [17], there is no doubt that it complexes the nitrosonium ion.

In the infrared spectra of the complexes formed between the aromatic compounds and the nitrosonium salt in acetonitrile, the band at 1850 cm^{-1} is absent; new bands appear at 1900 cm^{-1} and 1930 cm^{-1} for the pentamethylbenzene and durene complexes, respectively. The situation is similar to that which occurs in nitromethane. The observed decrease in frequency and increase in intensity of the N–O stretching vibration in the complexes are characteristics which have been found for other acceptor species [14] [18] in complex formation, and are consistent with the fact that the present complexes are molecular complexes.

A comprehensive evaluation of the IR. spectra is precluded by absorption of the solvent and of the anion, $\text{PF}_6^{\ominus}$. In order to examine the $880\text{--}840\text{ cm}^{-1}$ region of the spectrum, we formed complexes between the aromatic compounds and nitrosonium tetrafluoroborate in nitromethane by addition of a solution of the alkylbenzene to a suspension of the nitrosonium salt. The salt dissolved, and complexes similar to those obtained with nitrosonium hexafluorophosphate were formed. In the IR. spectra of the complexes (see Table 3), the bands representing the aromatic C–H

Table 3. *Infrared*^{a)} *spectra of pentamethylbenzene, durene, and their complexes with nitrosonium tetrafluoroborate, all in nitromethane at 20°*

Aromatic compound	Bands (cm^{-1}) ^{b)}	Bands (cm^{-1}) in the spectrum of the complex ^{d)}	
Pentamethylbenzene	870	1950–1860,	885
1-Deuteriopentamethylbenzene	745 745 ^{c)}	1950–1860,	750
Durene	870	1975–1900,	885
3,6-Dideuteriodurene	725 720 ^{c)}	1975–1900,	735
Mesitylene	840	2000–1950,	855, 840

a) Silver chloride cell, 0.5 mm path length.

b) Aromatic C–H out-of-plane bending frequency.

c) Potassium bromide disc.

d) Solution (0.1 M) of the aromatic compounds in nitromethane mixed with equal volume of a suspension (0.1 M) of the nitrosonium salt in nitromethane.

out-of-plane bending in the aromatic compounds are shifted slightly to higher wave numbers. No other bands are observed in this region for the complexes formed from the nitrosonium salt and durene and pentamethylbenzene, but in the case of the mesitylene complex two bands, at 840 cm^{-1} and 855 cm^{-1} , are present. Obviously, compared with durene and pentamethylbenzene, mesitylene is less complexed at equilibrium.

For durene, the appearance of only one band representing the C–H out-of-plane bending mode in the complex suggests that both aromatic protons are affected in the

same manner by complex formation *i.e.* the complex is symmetrical. It is likely that the complexes formed between the other alkylbenzenes and the nitrosonium ion are similar.

The PMR. spectra of the complexes formed in trideuterionitromethane are shown in Table 4.

Table 4. PMR. spectra^{a)} of pentamethylbenzene and durene, and their complexes with nitrosonium hexafluorophosphate all in trideuterionitromethane

Compound	Signals ^{b)} and assignments
Pentamethylbenzene ^{c)}	6.81 (S, 1, aromatic H); 2.21, 2.18 (S, 15, 5 methyl groups)
Durene ^{c)}	6.88 (S, 2, aromatic H); 2.18 (S, 12, 4 methyl groups)
Pentamethylbenzene ^{d)} + NOPF ₆	7.52 (S, 1, aromatic H); 2.44, 2.38 (S, 15, 5 methyl groups)
Durene + NOPF ₆ ^{d)}	7.42 (S, 2, aromatic H); 2.37 (S, 12, 4 methyl groups)
Pentamethylbenzene ^{e)} + NOPF ₆	7.1 (S, 1, aromatic H); 2.31, 2.27 (S, 15, 5 methyl groups)

^{a)} At 35°; solutions prepared at 20°.

^{b)} Chemical shift in ppm with reference to tetramethylsilane; abbreviations for assignments, see ⁴⁾.

^{c)} 0.4M.

^{d)} Equal volumes of 0.4M solutions mixed.

^{e)} 0.4M solution of pentamethylbenzene in deuterionitromethane mixed with equal volume of 0.2M solution of nitrosonium salt in deuterionitromethane.

The spectra of the complexes bear no relation to those of the protonated aromatic compounds [19], but are consistent with a π -type structure for the complexes. Thus the signals representing the aromatic protons and the methyl groups are shifted downfield on complex formation, but the splitting remains the same as in the uncomplexed compounds. In the presence of an excess of the alkylbenzene, this downfield shift is smaller. The rates of exchange between the two states of the aromatic compound are thus very fast, a fact which is in keeping with the postulated π -type structure of the complexes.

To summarize the situation therefore, both durene and pentamethylbenzene form symmetric, 1:1 molecular complexes with the nitrosonium ion in nitromethane and acetonitrile. Qualitative experiments indicate that all the methylbenzenes and benzene itself form complexes with nitrosonium salts in these solvents. At a fixed concentration of the reactants, the colour of the solution depends on the basicity (presumably π -basicity) of the aromatic compound. In the case of benzene, the solution is a light orange colour; only a small amount of complex is present at equilibrium.

With regard to the nature of the bonding between the electrophile and the aromatic compound, it is clear that in the present complexes no σ -bond is formed. The factors which contribute to the stability of molecular complexes are not fully understood [20], but it is likely that they depend on the nature of the donor and acceptor species, and the solvent [21]. Our present results do not allow a more detailed description of these complexes.

It may be noted, however, that the colours and UV. spectra of the present complexes are identical to those of the unknown addition complexes formed in the nitra-

tions with nitronium salts. Further similarities are noted and discussed in the next section.

3. Nitration of Durene and Pentamethylbenzene with Nitronium Salts in Nitromethane and Acetonitrile. — 3.1. *Nature of the Complexes formed in the Nitration.* The IR. spectra of the nitration solutions show the expected similarity to the spectra of the complexes formed between the aromatic compounds and the nitrosonium ion.

The IR. spectrum of nitronium hexafluorophosphate in nitromethane shows the expected O–N–O antisymmetric stretching vibration at 2360 cm^{-1} [22] and also a small band at 2260 cm^{-1} arising from the impurity, nitrosonium hexafluorophosphate.

For the nitrations of durene and pentamethylbenzene (0.4M) [1:1 mixed] in nitromethane at 20°C , the IR. spectrum shows an intense band at 1930 cm^{-1} in the case of durene and 1900 cm^{-1} in the case of pentamethylbenzene. In both cases, a band at 3400 cm^{-1} is observed which is shifted to 2550 cm^{-1} in the IR. spectra of the nitration solutions of the deuterio-compounds. We are unable to assign a particular mode to this band. The bands at 3400 cm^{-1} and ca. 1920 cm^{-1} disappear on quenching the nitration solutions with ammonia.

When the nitrations of the aromatic compounds (0.2M) are carried out with a suspension of nitronium tetrafluoroborate (0.2M) [1:1 mixed] in nitromethane at 20°C (cf. section 2.2), similar bands to those mentioned above are observed in the region of 1900 cm^{-1} . In the case of durene, a band is observed at 855 cm^{-1} which is typical of dinitrodurene; this band represents the O–N–O symmetric deformation in this compound. Recent work [23] favours this assignment in preference to the earlier view [24] that bands observed in the region of 850 cm^{-1} in the IR. spectra of aromatic nitro-compounds represent the C–N stretching frequency. Other bands of low intensities appear in this region, e.g. at 870 cm^{-1} and 835 cm^{-1} in the case of durene, and at 835 cm^{-1} for pentamethylbenzene. These bands are not shifted in the IR. spectra of the nitration solutions of the deuterio-compounds and we have not identified them.

The IR. spectrum of nitronium hexafluorophosphate in acetonitrile shows the salt forms a complex with the solvent. No band at 2360 cm^{-1} is observed, but three bands appear at lower wave numbers (1875 cm^{-1} , 1740 cm^{-1} and 1670 cm^{-1}). Therefore, nitrations were effected only with fresh solutions of the salt.

For the nitrations of durene and pentamethylbenzene (0.2M) with nitronium hexafluorophosphate (0.2M) [1:1 mixed] in acetonitrile at 20°C , the IR. spectra show the band at ca. 1920 cm^{-1} as found for the nitrations in nitromethane. Nitrations were not carried out with nitronium tetrafluoroborate.

The PMR. spectra of the nitration solutions are complicated; signals representing the nitro-compounds, by-products and the aromatic compounds are to be expected. Table 5 shows the results obtained for the nitration of pentamethylbenzene with nitronium hexafluorophosphate in trideutero-acetonitrile.

As for the complexes formed between the aromatic compounds and nitrosonium salts, the signal of the aromatic proton (7.4 ppm) is shifted downfield from the value found for the aromatic compound itself (6.88 ppm). When nitration is carried out in the presence of excess pentamethylbenzene [PMB (0.27M): NO_2PF_6 (0.135M); 1:1 mixed], this shift is smaller. With twofold excess of nitronium salt, the signal is absent from the PMR. spectrum of the nitration solution and the solution is colourless.

Table 5. PMR. spectrum^{a)} of pentamethylbenzene and the solution formed by mixing equal volumes of 0.27 M solutions of pentamethylbenzene and 0.27 M nitronium hexafluorophosphate, all in trideuterio-acetonitrile

Compound	Signals ^{b)} and assignments
Pentamethylbenzene	6.88 (S, 1, aromatic H); 2.24, 2.18 (S, 15, 5 methyl groups)
Pentamethylbenzene + NO ₂ PF ₆	9.1 (S broad, 1.5, acidic H); 7.4 (S, 0.3, aromatic H) 4.55 (poorly resolved signal, 0.4, methylene H) ^{c)} ; 2.1–2.5 (M, 13, methyl groups)

a) and b) are the respective footnotes in Table 4.

c) See text.

The resolution of the signal appearing at 4.55 ppm is poor, but on addition of D₂O the signal collapses to a singlet. There is no doubt that this signal arises from the methylene protons of the principal by-product formed in the reaction, N-acetyl-2,3,4,5-tetramethyl-6-nitrobenzylamine. The PMR. spectrum of this compound in CD₃CN shows a doublet ($J_{\text{CH}_2-\text{NH}} = 5$ Hz) centred at 4.55 ppm. On the addition of H₂SO₄, the resolution of this signal becomes very poor because of the enhancement of the rate of exchange of the N–H proton. However, when D₂SO₄ is added, the signal representing the methylene protons is a singlet at 4.55 ppm. The CH₂–N–D coupling constant is very small.

The signal at 9.1 ppm, representing an acidic proton, is shifted upfield on the addition of a small amount of water to the nitration solution. This signal is still observed in the PMR. spectrum of the nitration solution of 1-deuteriopentamethylbenzene.

The results from these studies of the IR. and PMR. spectra of the nitration solutions, together with the data from ultraviolet spectra, suggest that the complexes formed in the nitrations of these alkylbenzenes with nitronium salts in aprotic solvents are identical with the complexes formed between the aromatic compounds and nitrosonium salts. Thus the UV. spectra of both types of complex in acetonitrile show identical maxima, and the IR. spectra in nitromethane and acetonitrile show identical bands in the region of 1900 cm⁻¹. The PMR. spectrum of the nitration solution is consistent with the view that part of the aromatic compound is complexed, and part has lost a proton from a methyl group.

Obviously, the nitrosonium salts present in our samples of nitronium salts will form complexes with the aromatic compounds. However, under certain conditions of nitration, nitrous acid is produced in a secondary reaction leading to by-products [9]. This reaction involves proton loss from a methyl group, a step which certainly takes place under the present conditions¹⁾. The nitrous acid formed in the solution may undergo protonation, and displacement of water by PF₆[⊖] would lead to the formation of nitrosonium hexafluorophosphate which is capable of forming complexes with the alkylbenzenes.

¹⁾ In the nitration of pentamethylbenzene, tritiated in the methyl group in 1-position, with nitronium hexafluorophosphate in acetonitrile, tritium is lost [R. Renold, Diplomarbeit, ETH Zürich 1969].

We have assayed the nitrous acid present in the nitration solutions, and we have estimated the amount of complex present using data from the visible spectra of the solutions (results see Table 6).

Table 6. Nitration of durene and pentamethylbenzene with nitronium hexafluorophosphate^{a)} in nitromethane and acetonitrile, at 20°
(Equal volumes of solutions mixed)

	In nitromethane		In acetonitrile		
Pentamethylbenzene	0.2 M	0.02 M		0.2 M	
Nitronium hexafluorophosphate	0.2 M	0.02 M	0.2 M	0.2 M	0.2 M
Durene			0.2 M		0.2 M
Optical density of } nitration solution	650 nm	0.600 ^{b)}	0.505 ^{c)}	0.135 ^{b)}	0.362 ^{b)}
	600 nm	1.363 ^{b)}	1.142 ^{c)}	0.313 ^{b)}	0.872 ^{b)}
				0.352 ^{b)}	
% Complex ^{d)}	42.0	33.0	1.6	32.0	10.0
% HNO ₂ formed during the reaction	35.6	32.3	7.1	28.0	6.0
Products ^{e)} :					
Pentamethylbenzene	48.0%	40.1%		36.0%	
Pentamethylnitrobenzene	2.7%	19.2%		20.0%	
By-products ^{f)}	49.3%	40.7%	8.1%	44.0%	5.0%
Durene			47.0%		45.0%
Mononitrodurene			2.4%		15.0%
Dinitrodurene			42.5%		35.0%

a) Containing 11.0% nitrosonium hexafluorophosphate.

b) 0.1 cm cell.

c) 1 cm cell.

d) See text. The figure is a mean value for the two wavelengths.

e) Determined by gas-liquid partition chromatography; estimated error: $\pm 5\%$ of value shown.

f) By difference.

The figures for nitrous acid present in the system represent the nitrous acid formed during the reaction and were obtained by subtracting the amount of the impurity, nitrosonium hexafluorophosphate, present in the nitronium salt from the total nitrous acid.

In the calculation of the amount of complex formed from the nitrous acid produced, we were forced to make a number of assumptions. Equation (2) was used for the calculation. The results

$$[\text{Complex}] = \frac{\text{O.D. nitration sol.} - \text{O.D. init. compl.}}{2 \times \text{O.D. aromatic compound : NOPF}_6 \text{ complex (0.05M)}} \quad (2)$$

shown are a mean of determination at 650 nm and at 600 nm. O.D. init. compl. is the optical density of the complex formed between the aromatic compound and the nitrosonium salt impurity. We must assume (a) that all of this impurity forms a complex with the alkylbenzene, independently of the amount of the nitronium salt, and (b) that the figures shown in Table 6 for the optical densities of the complexes aromatic compound : NOPF₆ (0.1 M, 1 : 1 mixed) represent 100% complex. This latter assumption may be true for acetonitrile but in nitromethane it appears that, at this concentration, the equilibria (1) do not lie completely to the right. In these cases, we have used the values of the optical densities of the complexes formed between the aromatic compounds (0.5 M) and the nitrosonium salt (0.1 M) to represent 100% complex *i.e.* 0.05 M.

In view of these assumptions, only qualitative conclusions can be drawn concerning the amount of complex formed in the nitration. Larger amounts of nitrous acid and complex are formed in the nitration of pentamethylbenzene than in that of durene. We attribute this to the rôle of mixing of the reagents in nitrations of this kind. The pentamethylnitrobenzene formed in the nitration is attacked by the nitronium ion; a process (see below) which leads to the formation of by-products and an equivalent amount of nitrous acid. However, our results show that the amount of nitrous acid produced is always less than that of by-products. It is possible that some of the nitrous acid is lost either as nitric oxide or in some reaction with the by-products. For the nitration of pentamethylbenzene in nitromethane, a lowering of the initial concentrations of the reagents by a factor of ten reduces the percentage of by-products by a factor of ca. 1/5, and the amount of $\text{NO}^\oplus$, N_2O_4 , HNO_2 (determined as a whole as nitrous acid) by a factor of ca. 1/11. Thus there may be less destruction of $\text{NO}^\oplus$ by reaction with the by-products at the lower concentration, but we have no definite evidence for this.

The small amount of nitrous acid formed in the nitration of durene is understandable from the fact that durene can undergo dinitration. However, the calculated amount of complex formed in the reaction in nitromethane may be in error by a factor of 2–3 because of our uncertainty concerning the value of $\text{O.D.}_{\text{init. compl.}}$.

3.2. The Mechanism of the Nitration of Pentamethylbenzene with Nitronium Hexafluorophosphate. As stated before, in our opinion, the compositions of the final products in the nitrations of durene and pentamethylbenzene with nitronium salts in aprotic solvents depend on the mixing process. For the nitration of durene, evidence has been presented to support this statement [9]²⁾. In the present work, the ratio of dinitrodurene to mononitrodurene in the final product is shown to depend on the solvent, varying from 2.34 for nitration in acetonitrile to 17.8 for nitration in nitromethane (Table 6). The reactivity of the nitrating reagent in acetonitrile is lower and, when mixing is important, this will result in a lower value for the dinitrodurene to mononitrodurene ratio than that found, under the same conditions, in nitromethane.

A similar situation is found in the nitration of pentamethylbenzene; here, an attack by the nitrating agent on pentamethylnitrobenzene (which is formed initially) leads to by-products. For nitration in nitromethane, a decrease in the initial reactant concentrations of a factor of ten (from 0.2M to 0.02M) results in a decrease in the ratio by-products: pentamethylnitrobenzene from 18.2 to 2.12. This ratio is also decreased (from 18.2 to 2.2) when the solvent is changed from nitromethane to acetonitrile (with the same concentrations of the reactants). The similarity between the nitrations of these two alkylbenzenes is further shown by the fact that, at a reagent concentration of 0.2M, the ratios (dinitrodurene + by-products): mononitrodurene, and by-products: pentamethylnitrobenzene are virtually the same in both solvents.

The nature of the by-products formed in the nitration of pentamethylbenzene with nitronium hexafluorophosphate in acetonitrile at 20° supports the view that the mononitro-compound is further attacked by the nitrating agent (see Table 7).

²⁾ A theoretical treatment of the selectivity exhibited in reactions which do depend on rate of mixing has been presented and discussed in detail by Rys [25].

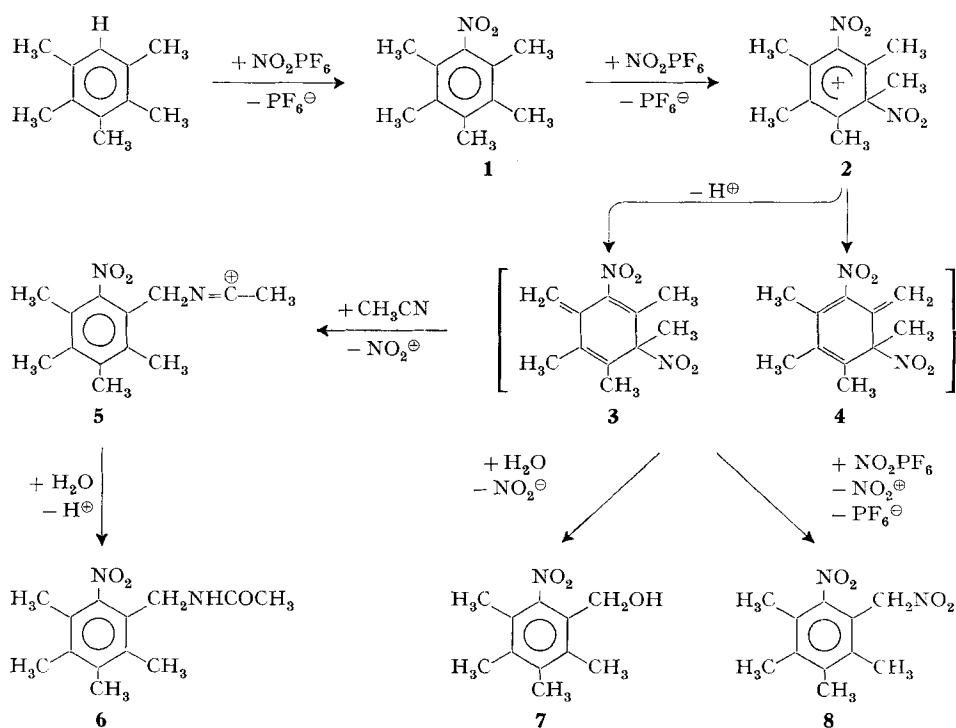
Table 7. Products formed in the nitration of pentamethylbenzene (0.2M) with nitronium hexafluorophosphate (0.2M) in acetonitrile at 20°
(Equal volumes of solutions mixed)

Product	Yield
Pentamethylbenzene	34%
Pentamethylnitrobenzene	20%
N-Acetyl-2,3,4,5-tetramethyl-6-nitro-benzylamine	38%
2,3,4,5-Tetramethyl-6-nitro-benzyl alcohol	1.5%
2,3,4,5-Tetramethyl-6-nitro-phenyl-nitromethane	1.0%
Total yield	94.5%

The products were isolated using column chromatography and identified by IR., PMR., and mass spectra. The proportions of the products were determined by weight and by gas chromatography using naphthalene as internal standard.

We propose the mechanism in Scheme 1 to account for the formation of pentamethylnitrobenzene (1) and the by-products of the reaction.

Scheme 1



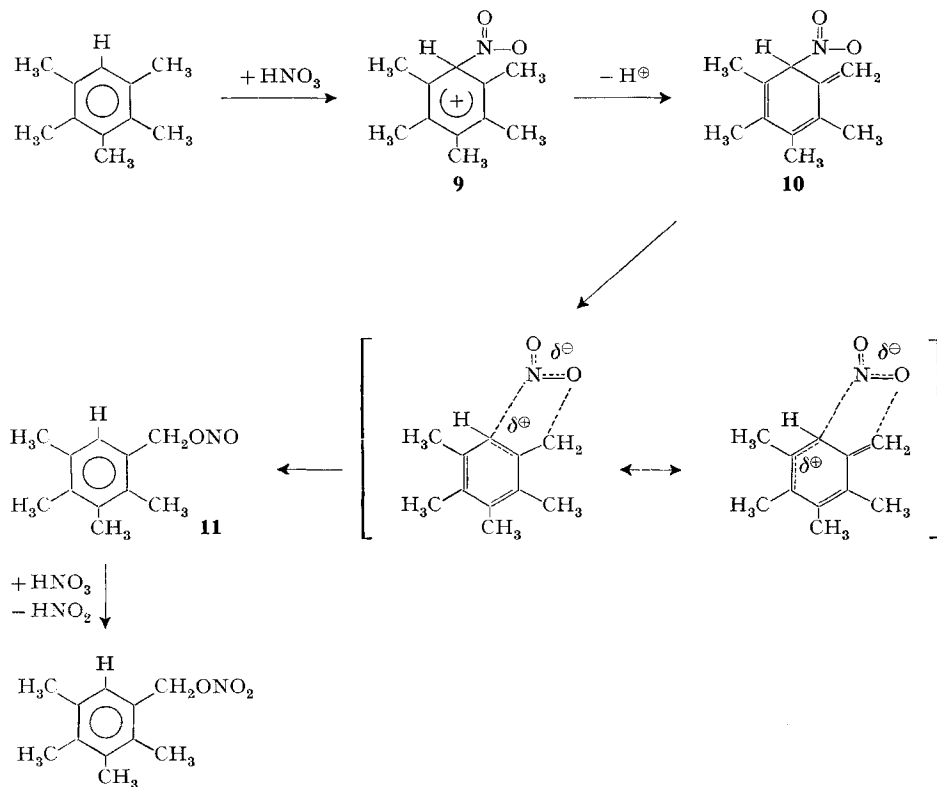
The attack by the nitronium ion on pentamethylnitrobenzene almost certainly occurs exclusively at a position *meta* to the nitro group; the complex **2** can be stabilized by two *ortho*-methyl groups and one *para*-methyl group. The PMR. spectrum of the nitration solution shows that a proton is lost from a methyl group; this process

results in the formation of the structures **3** and **4**. In all probability, the greater contribution comes from the *p*-quinonoid structure **3** [26]³⁾. **3** and/or **4** undergo a nucleophilic attack by the solvent with simultaneous release of a nitrite ion to give the carbonium ion **5**; this is hydrolyzed to N-acetyl-2,3,4,6-tetramethyl-6-nitrobenzylamine (**6**), the principal by-product.

Similarly, an attack by a water molecule gives 2,3,4,5-tetramethyl-6-nitrobenzyl alcohol (**7**). In addition, **3** and/or **4** may undergo electrophilic attack by the nitronium ion to form 2,3,4,5-tetramethyl-6-nitrophenyl-nitromethane (**8**).

The above intermolecular process is in contrast to the mechanism, in Scheme 2, proposed for the nitration of pentamethylbenzene with fuming nitric acid in chloroform or methylene chloride [27]. In this case, the main product is 2,3,4,5-tetramethylbenzyl nitrate (**11**). Some pentamethylnitrobenzene and a number of other by-products were isolated, but unfortunately these products seem not to have been

Scheme 2



determined. For these nitrations and for the nitration of pentamethylbenzene with fuming nitric acid in nitromethane, the above mechanism was proposed to account for the formation of the major by-product [28].

³⁾ We thank Dr. K. Schofield for drawing our attention to this fact.

It was recognised that the conversion of **9** into **11** may take place in two ways, either by a direct path or one involving the methylene cyclohexadiene intermediate (**10**). The authors did not express any preference for a particular path, but they considered unlikely an intermolecular mechanism such as we have proposed here [28].

For pentamethylbenzene, it is our opinion that nitration with nitronium salts must be distinguished from nitration with nitric acid or fuming nitric acid. In the former system, nitration is immeasurably fast, and under these circumstances the rate of mixing of the reagents becomes important. The pentamethylnitrobenzene formed initially reacts a second time with the nitrating agent, and in acetonitrile this process leads to the production of the amide **6** and other products. It is difficult to envisage an intramolecular process which is responsible for the formation of these by-products and nitrous acid.

In systems in which the concentration of the nitronium ion is very low, there is some evidence to suggest that nitrosation may be an important process in the nitration of durene and pentamethylbenzene. Autocatalysis has been observed in the nitrations, in nitromethane, of durene with nitronium hexafluorophosphate and water [9] and of pentamethylbenzene with fuming nitric acid [27]. Work is at hand in this laboratory concerning this problem.

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Experimental. – *Purification of Materials:* Nitromethane and acetonitrile were distilled twice in vacuo from P_2O_5 .

Aromatic compounds were recrystallised or distilled.

Nitronium salts: commercial products were dried under vacuum over P_2O_5 and stored in a desiccator.

Nitrosonium salts: commercial products were washed with sodium-dried benzene, dried, and then sublimed (80°/0.01 Torr).

Nitration of the alkylbenzenes with nitronium salts. All operations were carried out in a dry box. A weighed quantity of the aromatic compound contained in an air-tight tube, an empty tube of known weight and the appropriate solvent were introduced into the dry box. A quantity of the nitronium salt was transferred to the empty tube; this was removed from the dry box, reweighed, and returned to the box. The required amount of solvent was added to both tubes, and part of the solution of the nitronium salt was added to an equal volume of the solution of the aromatic compound by means of a pipette.

The complexes formed between the alkylbenzenes and nitrosonium salts were prepared similarly.

Spectroscopic measurements were made on solutions prepared in the above manner. UV. spectra were recorded using a Beckman Acta II spectrophotometer (absorption bands given in cm^{-1}); IR. spectra were recorded using a Perkin-Elmer 21 spectrophotometer (absorption bands given in nm), and PMR. spectra were obtained using a Varian A60 spectrometer.

Determination of nitrous acid: analysed following Rider & Mellon [29]. The optical density of the test specimen was measured at 524 nm and compared with a calibration chart prepared using standard solutions of sodium nitrite. Independent tests showed that the solvents used and the products formed in the reactions do not interfere.

Optical methods in which the coupling reaction is carried out at a high pH cannot be used to determine nitrous acid in the presence of nitromethane as this will couple with the diazonium ion.

The products formed in the nitration of pentamethylbenzene with nitronium hexafluorophosphate in acetonitrile. After nitration carried out in the manner described above, the solution was quenched

with ammonia and filtered. Evaporation of the filtrate gave a light-brown solid from which the organic material was extracted with hot chloroform. Filtration and removal of the solvent gave a solid which was extracted with carbon tetrachloride; this process separated most of the amide **6** which is virtually insoluble in carbon tetrachloride. Chromatography of the carbon tetrachloride extract gave the following products:

Pentamethylnitrobenzene (**1**): IR. (KBr): 2930 (CH_3 , C–H str.), 1530 and 1,375 (NO_2 , N–O str.), 840 (NO_2 , O–N–O bending). PMR. (in CDCl_3): 2.11 (S, 2)⁴; 2.20 (S, 3). Mass spectrum: M^+ at m/e 193.

N-Acetyl-2,3,4,6-tetramethyl-6-nitro-benzylamine (**6**): IR. (KBr): 3,260 ($\overset{\text{O}}{\parallel}\text{C}-\text{N}-\text{H}$, N–H str.), 2,900 (CH_3 , C–H str.), 1,640 ($\overset{\text{O}}{\parallel}\text{C}-\text{N}-\text{H}$, C=O str.), 1,525 and 1,375 (NO_2 , N–O str.). PMR. (in CDCl_3): 1.96 (S, 3, acetyl CH_3); 2.18 (S, 3, arom. CH_3); 2.28 (S, 6, arom. CH_3); 2.31 (S, 3, arom. CH_3); 4.32 (D, 2, CH_2); 5.5–6.0 (broad S, 1, N–H), $J_{\text{CH}_2-\overset{\text{H}}{\text{N}}} = 5$ Hz; Mass spectrum: M^+ at m/e 250.

2,3,4,5-Tetramethyl-6-nitro-benzyl alcohol (**7**): IR. (KBr): 3400 (OH, O–H str.), 2930 (CH_3 , C–H str.), 1530 and 1375 (NO_2 , N–O str.). PMR. (in CCl_4): 1.94 (S, 1, OH); 2.15–2.35 (M, 12, arom. CH_3); 4.40 (D, 2, CH_2)⁵; $J_{\text{CH}_2-\text{OH}} = 7$ Hz. Mass spectrum: M^+ at m/e 209.

2,3,4,5-Tetramethyl-6-nitro-phenyl-nitromethane (**8**): IR. (KBr): 2930 (CH_3 , C–H str.), 1575 (aliphatic NO_2 , N–O str.), 1530 (aromatic NO_2 , N–O str.), 1375 (aliphatic and aromatic NO_2 , N–O str.). PMR. (in CD_3COCD_3): 2.20 (S, 3, arom. CH_3); 2.36 (S, 9, arom. CH_3); 5.68 (S, 2, CH_2). Mass spectrum: M^+ at m/e 238.

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⁴) The number in brackets refers to the number of protons; the signals are singlets (S), doublets (D), or multiplets (M).

⁵) On the addition of deuteriated trifluoroacetic acid, the signal at 1.94 ppm disappears and the doublet at 4.40 ppm collapses to a singlet at 4.63 ppm.

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221. A Total Synthesis of the Alkaloid Rhoeadine

Preliminary communication¹⁾

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(29. VII. 71)

Zusammenfassung. Die Umwandlung des Phtalidisochinolins (–)-Bicucullin (**1**) in das Benzazepinalkaloid (+)-Rhoeadin (**8**) und in sein unnatürliches Isomeres werden beschrieben.

Based on model experiments for the preparation of benzazepines from the phthalide alkaloids (–)- α -narcotine¹⁾ [**1**] and (–)- β -hydrastine¹⁾, the phthalide-isoquinoline (–)-bicuculline (**1**) has been converted by a new, straightforward synthesis into the benzazepine alkaloid (+)-rhoeadine (**8**)³⁾ and its unnatural antipode. Since **1** was obtained from (–)- β -hydrastine⁴⁾ which has been previously synthesized [3], the following transformations⁵⁾ constitute the first total synthesis of natural rhoeadine⁶⁾.

Reaction of (–)-bicuculline (**1**) [m.p. 193–194°, $[\alpha]_D^{33} = -128^\circ$ ($c = 0.27$, CHCl_3); lit. [5]: m.p. 193–195°, $[\alpha]_D^{33} = -110^\circ$ ($c = 0.27$, CHCl_3)] with phenyl chloroformate and di-isopropylethylamine, followed by dehydrohalogenation with a mixture of dimethyl sulfoxide and di-isopropylethylamine yielded the urethane **2** (> 90% yield).

¹⁾ Details will be published in *Mh. Chem.*

²⁾ Visiting Professor, Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck, Austria.

³⁾ The formulas **6**, **7** and **8** show the absolute configurations as suggested by Šantavý for rhoeadine [2]. – *Added in proof:* The configurations given have in the meanwhile been verified by X-ray study of rhoeagenine methiodide being published in *Acta crist.* (personal communication by C. S. Huber, Biochem. Lab., National Research Council, Ottawa 7, Canada).

⁴⁾ Details will be published elsewhere.

⁵⁾ All isolated compounds gave acceptable elemental analyses. Unless noted otherwise, the UV. spectra were measured in ethanol, the IR. spectra were determined in a KBr pellet and the NMR. spectra were obtained using CDCl_3 as solvent.

⁶⁾ The synthesis of a ($\pm$)-rhoeadine precursor from a *spiro*-isoquinoline has been recently reported [4].