Substituent Effects in the Electrophilic Substitution of Deactivated Systems. Part II.[1] The Mills–Nixon Effect and the Nitration of Strained 1,2,3,4-Tetrahydroquinolinium Ions

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Second-order rate coefficients have been measured for the nitration in 82% aqueous sulphuric acid of a series of strained 2-alkyl-1-methyl- and 2-alkyl-1,4-dimethyl-tetrahydroquinolines. Product analysis reveals the surprising absence of 5-nitro-compounds and this, together with variations in the ratios of 6- to 7-nitrated products, is consistent with the explanation of the Mills–Nixon effect in terms of strain in bonds common to fused rings. Varying initial state strain does not appreciably affect the overall rate of nitration.

THE nitration of deactivated molecules is a useful system for a general study of substituent effects for a number of reasons. The rate of nitration of such molecules has been shown to be very susceptible to substituent effects [1] confirming that the relevant transition state is closer in structure to the σ-intermediate than it is with more reactive substrates. In addition the mechanism of nitration in aqueous sulphuric acid is well understood and for deactivated systems reactivity is directly measurable without recourse to possibly misleading competition experiments.[2]

We here report the results of product and reactivity studies of the nitration of the ions (1) and (2) which were undertaken with a view to deciding between current explanations of the Mills–Nixon effect.[3] The principle behind this attempt was that strain in the fused saturated ring could be varied considerably by varying the C(2) substituent. For both series of ions steric hindrance due to the C(4) substituent is constant. This is not the case for previously discussed examples of the Mills–Nixon effect where ring strain is thought to vary as a function of the size of the fused ring.

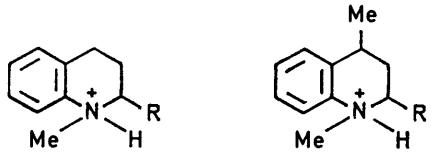
The best known examples of the Mills–Nixon effect relate to indane and tetralin where the products of bromination [3c] and the reactivity towards protodesilylation and protodetritiation [3g] strongly favour the β-position in indane but hardly discriminate in tetralin.

[1] Part I, J. H. P. Utley and T. A. Vaughan, *J. Chem. Soc.* (*B*), 1968, 196.

[2] R. G. Coombes, R. B. Moodie, and K. Schofield, *Chem. Comm.*, 1967, 352.

[3] (*a*) W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 1930, 2510; (*b*) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, 1946, **42**, 756; (*c*) J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, 1965, **21**, 1665; (*d*) J. Vaughan and G. J. Wright, *J. Org. Chem.*, 1968, **33**, 2580; (*e*) R. Taylor, G. J. Wright, and A. J. Holmes, *J. Chem. Soc.* (*B*), 1967, 780; (*f*) R. Taylor, *J. Chem. Soc.* (*B*), 1968, 1559; (*g*) A. R. Bassindale, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.* (*B*), 1969, 12; (*h*) R. Taylor, M. P. David, and J. F. W. McOmie, *J.C.S. Perkin II*, 1972, 162.

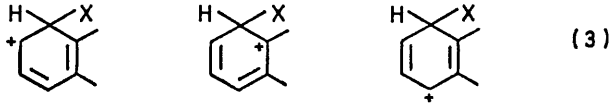
The reactivity data suggest a deactivation at the α-position of indane and this is currently explained in terms of strain in the transition state for α-substitution, or by electron withdrawal from the α-position due in



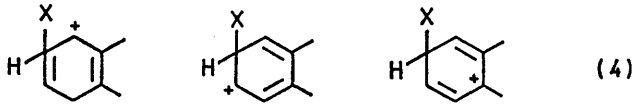
(1) R = H,Me,Et,Pr^i, Bu^t or Me$_2$ (2) R = H,Me,Et or Bu^t

indane to increased *s*-character in the bond linking C(1) and the aromatic ring.[4] This change in *s*-character is associated with the smaller internal ring angle in indane.

The strain theory supposes that relative bond lengths in the transition states to be compared can be estimated from a consideration of the major canonical forms contributing to the hybrid σ-intermediates (3) and (4).



(3)



(4)

An explanation of the Mills–Nixon effect follows if it is assumed that the fused five-membered ring resists shortening of the common bond, whereas the six-membered ring does not.

RESULTS AND DISCUSSION

The Species Nitrated.—The *N*-methyltetrahydroquinolines were nitrated at 0 °C with potassium nitrate in 82% (w/w) sulphuric acid. It is almost certain that in these conditions reaction involves only the protonated base. The pK_a of 1,2,3,4-tetrahydroquinoline [5] is 5·03 and for 82% sulphuric acid the primary amine acidity function [6] is −7·66. Use of these values in the usual equation leads to the conclusion that only one molecule in $8{\cdot}38 \times 10^{12}$ is present as the free base. The *N*-methyltetrahydroquinolines will, by analogy with *N*-methyl- and *NN*-dimethyl-*o*-toluidine, be more basic by *ca.* 1 pK_a unit. The tertiary amine acidity function [7] in 82% sulphuric acid is *ca.* −9·7. Thus for 1-methyl-1,2,3,4-tetrahydroquinoline in 82% sulphuric acid the free base : conjugate acid ratio is in the region of 10^{-15}—10^{-16}.

From use of the method described [8] by Ridd *et al.* and an approximate value for the viscosity of 82% sulphuric acid of 0·22 cP the bimolecular encounter rate at 25 °C is $1{\cdot}8 \times 10^{10}$ l mol^{-1} min^{-1}. Thus the maximum possible rate of reaction involving the free base is obtained by multiplying by 10^{-15}, *i.e.*, 3×10^{-5} l mol^{-1} min^{-1}. In reality the maximum rate will be even lower because nitric acid is not completely converted into nitronium ion in 82% sulphuric acid. The second-order rate coefficient for nitration of 1-methyl-1,2,3,4-tetrahydroquinoline in 82% sulphuric acid is 9·8 l mol^{-1} min^{-1} at 5 °C. It is unlikely therefore that a significant proportion of products arises *via* nitration of the free base.

Position of Nitration.—The mononitrated products were liberated by quenching in aqueous alkali and the crude reaction mixtures were analysed by separation by t.l.c. and column chromatography followed by weighing of the isolated fraction. Where sufficient material was recovered the fractions were confirmed as mononitro-isomers by elemental analysis. The position of nitration was ascertained by comparison of u.v. and n.m.r. spectra with those of authentic specimens. The n.m.r. absorption of the aromatic ring protons was particularly useful in identifying the position of nitration and the u.v. spectra of the 6-nitro-isomers showed the high $\lambda_{max.}$ values (410 nm) and extinction coefficients characteristic of compounds with a *p*-nitroaniline-type structure. Recovery of material put on columns and plates was always >90% and by use of an artificial mixture of authentic isomers the method was shown to be capable of detecting and measuring a low percentage of any of the isomers. Details of the procedures are given in the Experimental section.

TABLE 1

Products of nitration of 1-methyl-1,2,3,4-tetrahydroquinolinium ions [a]

2-Alkyl series

2-Substituent	H	Me [b]	Et	Pr^i	Bu^t [c]	Me$_2$
7-Isomer (%)	71	81	61	83	69	89
6-Isomer (%)	23	9	18	8	4	8

2-Alkyl-4-methyl series

2-Substituent	H	Me	Et	Bu^t [d]
7-Isomer (%)	65	88	80	75
6-Isomer (%)	15	8	15	1

[a] Duplicate experiments were performed and the values quoted are judged accurate to ±5% of the figure given. Minor products (<5%) are not recorded. [b–d] Unidentified products: *b*, 7%; *c*, 11%; *d*, 13 and 7%.

The amounts of identified products are expressed as a percentage of the weight of material recovered from the plate or column. These results are summarised in Table 1 from which two noteworthy features emerge. The first is the absence of significant amounts of the 5-nitro-isomers. This position is *meta* to the positive

[4] A. Streitwieser, jun., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, 1968, **90**, 1357.

[5] R. Adams and J. Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2584.

[6] H. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, 1963, **85**, 878.

[7] E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, 1966, **88**, 1177.

[8] M. W. Austin and J. H. Ridd, *J. Chem. Soc.*, 1963, 4204.

nitrogen pole and is the equivalent of the α-position in tetralin and indane. By separation of an artificial mixture of isomers, including the 5-nitro-compound, it was shown that amounts of >5% would have been detected with ease. Similarly the 8-isomer, if present, would have been detected.

The second point of interest is the reduction in the proportion of 6-isomer for the compounds with 2-substituents. The extent of nitration at the 7-position is little affected by the nature of the 2-substituent.

These conclusions would be upset if the unidentified products referred to in Table 1 were derived from subsequent reactions of the mononitro-isomers. This is unlikely however because in a control experiment (see Experimental section) the 5-, 6-, and 7-nitro-compounds were found to be stable to the solvent and work-up conditions. Further, although the nitrating agent was not present in excess, if the unidentified products came from further nitration or oxidation of the 6-isomer the characteristic position of u.v. absorption (410 nm) would be preserved. The unidentified products listed in Table 1 have $\lambda_{max.}$ values in the region of 260 nm which suggests further reaction of the 7-nitro-isomer (unlikely for the reasons given) or nitration *meta* to the nitrogen pole involving an oxidation product of the starting tetrahydroquinoline (more likely).

Rate of Nitration.—The results of the kinetics experiments are summarised in Table 2, due allowance having been made for the product distribution. It is apparent that, whereas there is no marked variation in the overall rate due to 2-substitution, separation into coefficients for 6- and 7-nitration indicates a drop in reactivity at the 6-position for the ions with large 2-substituents.

TABLE 2

Second-order rate coefficients/l mol^{-1} min^{-1} for the nitration of 1-methyl-1,2,3,4-tetrahydroquinolinium ions [a]

2-Alkyl series

2-Substituent	H	Me	Et	Pr^{i}	Bu^{t}	Me$_2$
k (overall)	9·8	15·3	11·0	9·0	8·7	14·5
k_7	7·2	12·4	6·7	7·5	6·0	13·0
k_6	2·3	1·4	2·1	0·72	0·37	1·3
k_7/k_6	3·1	8·9	3·2	10·5	16·2	10·0

2-Alkyl-4-methyl series

2-Substituent	H	Me	Et	Bu^{t}
k (overall)	5·2	9·5	7·0	7·0
k_7	3·4	8·3	5·6	5·3
k_6	0·83	0·76	1·1	0·09
k_7/k_6	4·1	10·9	5·0	59

[a] 82·1% H_2SO_4 at 5·0 °C.

This is reflected in a higher $k_7 : k_6$ ratio. For a given 2-substituent the overall rate of nitration is lower for the 4-methyl series.

Alkyl-group substitution would be expected to influence the position and rate of nitration for one or more of the following reasons: (i) steric strain could increase or decrease in going to the transition state, (ii) solvation of the initial or transition state could be inhibited, and (iii) the electron-releasing effect of the methylene groups of the alicyclic ring might be dependent on conformation.

One condition for (iii) to be important is that the hybridisation and therefore electronegativity of the bond linking C(4) to the aromatic ring changes significantly with conformation. This point will be further discussed below. Alternatively C–H hyperconjugation might contribute to electron release from the C(4) group and this would depend on the angle between the C–H bonds and the π-molecular orbital of the aromatic ring. It has been shown, however, that for the nitration of 4-alkylphenyltrimethylammonium ions electron release is in the inductive order.[1]

It is unlikely that steric inhibition of solvation accounts for the suppression of 6-nitration for bulky 2-substituents. Of the two positive charges on the transition state, solvation associated with the one delocalised over the aromatic ring will not be inhibited more for 6- than for 7-nitration. Inhibition of transition-state solvation might explain the rate difference between nitration of the 4-H and 4-Me series although the effect is very small. Solvation of the N–H bond of the nitrogen positive pole is likely to be important and likely to be inhibited by bulky 2-substitution. Ridd and his co-workers [9] have demonstrated that for compounds with positive pole substituents reactivity differences between *meta*- and *para*-substitution are not great and, further, reactivity is dictated largely by the direct field effect. Dispersal of charge by solvation therefore increases reactivity and this provides an explanation for the greater reactivity of the anilinium ion *vis à vis* the trimethylanilinium ion. However, for *N*-methylanilinium ions the *para* : *meta* ratio is decreased in an unexplained way by increased methylation at the nitrogen pole.[10] One explanation of this decrease in *para*-substitution involves inhibition of solvation of the positive pole. In the tetrahydroquinolinium ions such inhibition by 2-substituents would likewise result in a decrease in 6-substitution. The significant drop in 6-substitution is, however, sudden and consequent upon 2-t-butyl substitution. Further, although the difference is not great it is most noticeable for the 2-t-butyl-4-methyl substituted ion. It is unlikely that 4-methyl substitution would greatly affect solvation along the axis of the $^{+}$N–H bond. For these reasons we prefer at the moment an explanation in terms of (i), *i.e.*, steric-strain differences in the transition states leading to 6- and 7-substitution.

Initial-state Strain.—The ions (1) and (2) were chosen for study because it was believed that significant strain would be introduced by 2- and 4-substitution. The strain can be roughly estimated by use of Dreiding models by summing, in the usual way, unavoidable interactions in available staggered conformations. Half-chair conformations are assumed with 2-substituents equatorial. The result of the estimates of

[9] T. A. Modro and J. H. Ridd, *J. Chem. Soc.* (*B*), 1968, 528.
[10] M. Brickman, J. H. P. Utley, and J. H. Ridd, *J. Chem. Soc.*, 1965, 6851.

strain are given in Table 3. The *cis*-2-alkyl-4-methyl-1,2,3,4-tetrahydroquinolinium ions would be expected to be more strained than the corresponding 2-alkyl compounds by about one *gauche* interaction, that between the equatorial 4-methyl group and the adjacent C(5) group. The reasons for assigning *cis*-stereochemistry to these ions are given in the Experimental section.

TABLE 3

Estimated strain energy in 2-alkyl-1,2,3,4-tetrahydroquinolinium ions

Alkyl group	H	Me	Et	Pr^{i} [a]	Bu^{t} [b]	Me_2 [c]
Number of *gauche* interactions	0	1	2	3+	3+	2+
Relative strain/kcal mol^{-1}	0	0·9	1·8	3·6	*ca.* 6·4	2·7

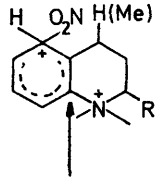
[a] 3 *gauche* + one 1,3-Me · · · H interaction (≡ 0·9 kcal mol^{-1}). [b] 3 *gauche* + one 1,3-Me · · · Me interaction (≡ 3·7 kcal mol^{-1}). [c] 2 *gauche* + one 1,3-Me · · · H interaction.

There is some direct experimental evidence for the considerable strain in some members of the series. (i) Decomposition products only were obtained following catalytic hydrogenation of 1,2-dihydro-2-isopropyl-1,4-dimethylquinoline, and the corresponding 2-t-butyl compound, in ethanol at 50 °C under 20 atm. of hydrogen. This method of hydrogenation worked well for the dihydroquinolines with less bulky 2-substituents. Hydrogenation under milder conditions allowed the preparation of the required tetrahydroquinolines. (ii) Using procedures which work well for other compounds in the series we could not prepare the methiodide of 1,4-dimethyl-2-t-butyl-1,2,3,4-tetrahydroquinoline.

Without strong belief in the precision of the values in Table 3 it can be concluded that transition states for nitration will adopt structures minimising conformational strain of this magnitude.

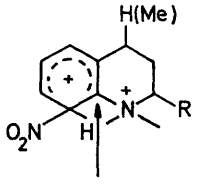
Transition States for 5- *and* 8-*Nitration*.—The very large alkyl group substituent effects found for nitration of 4-alkylphenyltrimethylammonium ions suggests that the transition state for deactivated systems is well advanced and that the usual assumption concerning its resemblance to the σ-intermediate is justified in these cases. Consequently the transition states for 5- and 8-nitration can be represented as (5) and (6) respectively. The bond orders for the bond common to the two rings follow if it is assumed that the three possible canonical forms contribute equally to the resonance hybrid. It is dangerous to apply this assumption generally as it is likely that canonical forms placing the positive charge near to the positive nitrogen pole will be disfavoured. Both 8- and 6-substitution involve a canonical form with positive charges on adjacent atoms and for this reason it is likely that in (6) the bond order of the common bond is greater than the estimate obtained in a simple manner. The bond orders can be used as a guide to lengthening or shortening of the common bond in going to the transition state.

The absence of significant amounts of the 5- and 8-isomers can now be explained. Substitution at the 8-position (*ortho* to the nitrogen pole) will be discouraged on electrostatic grounds but apart from this reason both the 5- and 8-positions resemble the hindered



Bond order 1·67 (bond shortening)

(5)

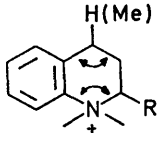


Bond order > 1·67 (considerable bond shortening)

(6)

peri-positions of polycyclic hydrocarbons. Further, although substitution into the corresponding position of tetralin is allowed, the more advanced carbon–nitrogen bond development in transition states for nitration of deactivated substrate means that such steric hindrance is more serious. Even for nitration of reactive substrates, where bond development in the transition state is less advanced, substitution at the α-position may be suppressed by fused *ortho*-substituents. For example, nitration of tetralin (0—2 °C, HNO_3–H_2SO_4–nitromethane) gives approximately equal amounts of the α- and β-mononitrotetralins whereas only 3% of the α-isomer is obtained by nitration of benzobicyclo[2,2,2]octene.[11]

An additional, or alternative, explanation is related to the strain hypothesis applied to the Mills–Nixon effect. The conformational strain referred to in Table 3 will be accommodated by distortions of torsion and ring angles resulting in a flattened alicyclic ring with internal angles increased in the manner depicted in



(7)

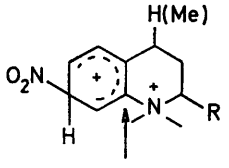
(7). Clearly lengthening of the bond common to both rings will relieve such strain and shortening of the bond will make it more severe. The common bond is shortened relative to the initial state in transition states (5) and (6).

Transition States for 6- *and* 7-*Nitration*.—These transition states must be considered with a view to recognising a factor or factors which will explain the deactivation towards 6-substitution for the more highly strained tetrahydroquinolinium ions. The rate of 7-nitration varies little with 2-substitution.

The transition state for 7-nitration may be depicted by (8) in which the common bond has lengthened compared with the initial state. There is therefore

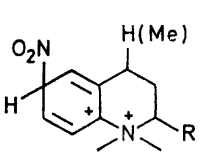
[11] H. Tanida and R. Muneyuki, *Tetrahedron Letters*, 1964, 2787.

no increase in strain in going to the transition state and consequently no deactivation of the 7-position in the strained substrate. The relief of strain due to bond lengthening must be similar for all members of the series or a relative steric acceleration would be observed.



Bond order 1·33
(bond lengthening)
(8)

The canonical structures to be considered for the transition state for 6-substitution are given in (9)—(11). Structure (9) will for polar reasons be of higher energy than the others although its contribution to the resonance hybrid would lengthen the common bond and thus allow relief of conformational strain. For a large 2-substituent therefore the transition state leading to



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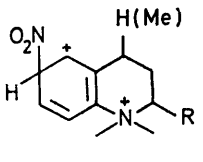

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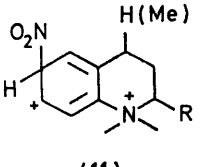

(11)

7-nitration is likely to accommodate conformational strain without requiring an unfavourable charge distribution whereas 6-nitration leads to a transition state in which steric strain can be accommodated only at the expense of raising the polar contribution to the total energy.

We do not believe that Streitwieser's explanation [4] of the enhanced acidity and decreased reactivity towards electrophiles of the α-position in fused ring systems can apply here. The cases in which such effects are observed involve fused rings in which the strain is associated with *decreased* internal ring angles. In our systems, the probably *increased* internal ring angles would, according to Streitwieser's hypothesis, mean higher *s*-character in the atomic orbitals used to construct the fused ring and therefore the α-carbon would be bound to an orbital of lower *s*-character and lower electronegativity. Such an effect, if significant, would by the inductive effect increase the relative reactivity of the 6-position in highly strained tetrahydroquinolinium ions.

EXPERIMENTAL

2-Alkyl-1-methyl-1,2,3,4-tetrahydroquinolines.— 1-Methyl-1,2,3,4-tetrahydroquinoline was obtained by methylation of commercial tetrahydroquinoline with trimethyl phosphate. The corresponding 2-alkyl derivatives were prepared by hydrogenation of the 1,2-dihydroquinolines which in turn were prepared by reaction between *N*-methylquinolinium iodide and the appropriate Grignard reagent. Typical experiments are described below and relevant physical properties of the compounds are summarised in Table 4.

1,2-Dihydro-1,2-dimethylquinoline.—Powdered quinoline methiodide (54 g, 0·20 mol) was added to a stirred solution of methylmagnesium iodide which had been prepared from magnesium (10 g) in ether (250 ml). When the reaction was complete, any excess of Grignard reagent was destroyed with water and concentrated hydrochloric acid was added until two clear layers separated. Ammonium chloride (7 g) and ammonia (*d* 0·880) solution was added until the solution was alkaline. The ether layer was separated, washed with water (2 × 70 ml), and dried (KOH). The product was worked-up in the usual way, b.p. 78—88 °C at 0·7 mmHg (lit.,[12] b.p. 70 °C at 0·6 mmHg), yield 20 g (90%).

1,2-Dimethyl-1,2,3,4-tetrahydroquinoline.— 1,2-Dihydro-1,2-dimethylquinoline (16 g, 0·1 mol) was dissolved in ethanol (75 ml) and Adams catalyst (90% PtO_2; 100 mg) was added. The starting material was hydrogenated at 50 atm of hydrogen and 50 °C for 24 h in a rocking autoclave. The catalyst was filtered off and the product worked-up in the usual way, b.p. 85—95 °C at 0·7 mmHg; yield 11 g (67%).

2-Alkyl-1,4-dimethyl-1,2,3,4-tetrahydroquinolines.— These compounds were prepared by essentially the route described above. The hydrogenation of 1,2-dihydro-1,4-dimethyl-2-t-butylquinoline presented difficulties and the original procedure gave a glutinous solid from which no amine could be distilled. Hydrogenation was therefore carried out in acidic solution in the manner described. Relevant physical properties of the compounds are summarised in Table 5.

1,2,4-Trimethyl-1,2,3,4-tetrahydroquinoline.—1,2-Dihydro-1,2,4-trimethylquinoline (7 g, 0·0404 mol) was dissolved in ethanol (25 ml) and Adams catalyst (90% PtO_2; 100 mg) was added. The starting material was hydrogenated at 50 atm of hydrogen and 50 °C for 24 h in a rocking autoclave. The catalyst was filtered off and the product isolated in the usual way (b.p. 102 °C at 0·6 mmHg); yield 4·8 g (68%).

G.l.c. (Varian Aerograph A90) on a Carbowax 20 M column at 195 °C with a helium flow rate of 70 ml min^{-1} showed that the product consisted of two fractions, the larger fraction being *ca.* 95% of the total.

The amine was dissolved in a minimum of dilute hydrochloric acid and picric acid (saturated solution in ethanol) was added until no more of the picrate was precipitated. The picrate was recrystallised three times from ethanol. The recrystallised picrate was dissolved in ethanol and dilute sodium hydroxide was added until the solution was slightly alkaline. The solution was shaken with ether, the aqueous layer was removed, and the ether layer washed with water until it was colourless. The ether layer was dried ($MgSO_4$) and worked up in the usual way; m.p. (picrate) 140—142 °C; b.p. (small-scale distillation; pot-temperature) 122 °C at 0·5 mmHg. G.l.c. (same conditions as above) of the recovered amine showed only one peak, the retention time of which was identical to that of the major peak in the original mixture.

1,4-Dimethyl-2-t-butyl-1,2,3,4-tetrahydroquinoline.— 2-t-Butyl-1,2-dihydro-1,4-dimethylquinoline (2 g, 0·009 mol)

[12] W. Bradley and S. Jeffrey, *J. Chem. Soc.*, 1954, 2770.

was dissolved in a 1 : 2 mixture of ethanol and fluoroboric acid (42% w/w HBF_4) (75 ml). Adams catalyst (100 mg) was added and hydrogenation was accomplished in a conventional apparatus at atmospheric pressure and room temperature. Following filtration and basification the product was worked-up in the usual manner; b.p. (small-scale distillation; pot-temperature) 150 °C at 0·5 mmHg; yield 0·8 g (81%).

more stable *cis*-isomer with the 2- and 4-substituents in equatorial positions. (ii) The chemical shifts for the 4-methyl group (Table 6) are similar for picrates of several members of the series which confirms that the stereochemistry is the same in this group of compounds. Further, the similarity of chemical shift for the 4-Me group between the 2-alkyl compounds and the corresponding unsubstituted derivative implies that throughout the 4-methyl

TABLE 4

2-Alkyl-1-methyl-1,2-dihydro- and 1,2,3,4-tetrahydroquinolines

			Methiodide							
				Found (%)				Calc. (%)			
R	Yield (%)	B.p.[a]/°C at (*p*/mmHg)	M.p./°C	C	H	N	I	C	H	N	I
1,2-Dihydro-derivatives											
Me	90	78—88 (0·7)									
Et	72	84 (0·6)									
Pr^i	54	94 (0·8)									
Bu^t	46	100—104 (1·7)									
Me_2	59 [b]	118—120 (0·5)									
1,2,3,4-Tetrahydro-derivatives											
Me	67	85—95 (0·7)	197—197·5	47·7	5·8	4·5	42·1	47·5	6·0	4·6	41·9
Et	69	82—102 (0·7)	158—160	49·2	6·3	4·1	40·2	49·2	6·4	4·4	40·0
Pr^i	90	88—94 (1·5)	180—182	50·7	6·5	4·5	38·1	50·8	6·7	4·2	38·3
Bu^t	90	100—104 (1·5)	162	52·1	7·2	4·1		52·2	7·0	4·1	
Me_2	79 [c]	130 (0·5)									

[a] Hot-box temperature for short-path distillation. [b] Prepared from 2-methylquinolinium iodide. [c] Hydrogenated in acidic solution (HBF_4–EtOH) by procedure described in text.

Stereochemistry of 2-Alkyl-1,4-dimethyl-1,2,3,4-tetrahydroquinolines.—The stereoisomers used in this investigation were the major (95%) products of hydrogenation of the

TABLE 5

2-Alkyl-1,4-dimethyl-1,2-dihydro- and 1,2,3,4-tetrahydroquinolines

R	Yield (%)	B.p.[a]/°C at (*p*/mmHg)
1,2-Dihydro-derivatives		
H	70 [b]	112 (1·5)
Me	27	86 (0·05)
Et	80	118—120 (1·0)
Pr^i	35	88—90 (0·15)
Bu^t	30	102 (0·2)
1,2,3,4-Tetrahydro-derivatives		
H	77	108 (0·5)
Me	68	122 (0·5) (picrate, m.p. 140—142 °C)
Et	58	127 (2) (picrate, m.p. 126—127 °C)
Bu^t	81 [c]	150 (0·5)

[a] Hot-box temperature for short-path distillation. [b] Prepared by potassium borohydride reduction of 4-methylquinolinium methiodide. [c] Prepared by hydrogenation in acidic solution (HBF_4–EtOH).

appropriate 1,2-dihydro-compounds. The major products were purified by crystallisation of their picrates and the amines subsequently recovered were, according to g.l.c., single compounds. We have assigned *cis*-stereochemistry to the compounds for the following reasons. (i) The conditions for hydrogenation were not mild (Pt, 50 °C, 50 atm of H_2, 24 h) suggesting that the major product is the group is in the preferred equatorial position. If the 2- and 4-substituents were *trans* the conformation equilibrium would ensure that the 4-methyl group signal was displaced according to the amount of axial conformer present. For the *trans*-2,4-dimethyl compound the axial component would be *ca.* 50% and this would probably result in a downfield shift [13] of *ca.* 4 Hz. (iii) The chemical shifts for the 4-methyl group in a series of 2-alkyl-1,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinolines are also similar (Table 6). It is unlikely that this would be the case if the compounds were the *trans*-isomers because this would imply that a pseudo-axial (R = Bu^t) and pseudo-equatorial (R = H) 4-methyl group displayed no difference in chemical shift.

Preparation and Characterisation of Authentic Samples of 5-, 6-, 7-, and 8-Nitro-compounds.—5- and 7-Nitroquinoline. These were prepared by the Skraup method [14] starting from *m*-nitroaniline. The mixture of nitroquinolines was dissolved in boiling aqueous nitric acid (*ca.* 10%). On cooling 5-nitroquinoline nitrate separated and after filtration and regeneration in concentrated ammonium hydroxide 5-nitroquinoline (m.p. 71—72 °C) was recrystallised from ether.

The acidic filtrate was made alkaline and the precipitate collected and dried. Boiling with light petroleum (b.p. 40—60 °C) extracted the 7-nitroquinoline (m.p. 135—136 °C) which was crystallised from ethanol.

1-Methyl-5-nitro-1,2,3,4-tetrahydroquinoline. 5-Nitroquinoline methiodide (5 g, 0·016 mol) was dissolved in 50% aqueous ethanol (25 ml) and added slowly to a solution of potassium borohydride (2 g, 0·037 mol) in 50% aqueous

[13] C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, 1960, **33**, 1257.

[14] L. Bradford, T. J. Elliott, and F. M. Rowe, *J. Chem. Soc.*, 1947, 437.

ethanol (50 ml). During the addition, the reaction mixture was kept under nitrogen. After 30 min, during which the mixture was stirred, ice-cold water was added and a red solid precipitated. The solid was filtered off and dried in a vacuum desiccator. The crystals were orange plates with a golden-red lustre, rapidly turning black on exposure to air (m.p. 57·5—60 °C; yield 2·6 g), δ (CCl_4) 6·3—7·0 (3H, m, ArH), 2·7 (3H, s, NMe), 3·9—4·1 (2H, 2 × d, 2-H_2), 5·5—5·9 (1H, 2 × t, 3-H), and 6·5—6·8 (1H, d, 4-H).

TABLE 6

Chemical shifts [a] for 4-Me group in 2-R-1,4-dimethyl-7-X-1,2,3,4-tetrahydroquinolines

X	H	H	H	NO_2	NO_2	NO_2	NO_2
R	H [b]	Me [b,c]	Et [b]	H [d,e]	Me [d]	Et [d]	t-Bu [d]
Shift/Hz	86	87	89	(80,77)	81	81	81

[a] Mid-points of doublets (J 6·5—7·0 Hz). [b] Picrates in $CDCl_3$. [c] 4-Methyl signal identified by irradiation at 2-proton signal (δ 4·05 p.p.m.). [d] Free bases in CCl_4. [e] The n.m.r. spectrum of this compound has several unusual features. The 4-methyl group gives rise to a pair of 1 : 1 doublets which, together, integrate for three protons against the aromatic proton signals. The spectrum of the aromatic protons is characteristic of 7-substitution and does not suggest the presence of any significant amount of isomeric impurity. The *N*-methyl signal is about 0·2 p.p.m. upfield of that for other members of the series. It is tempting to speculate that for this compound the half-chair to half-chair inversion is slow on the n.m.r. time scale so that separate signals are observed for pseudo-axial and pseudo-equatorial 4-methyl groups. Alternatively the effect may be a result of the intrinsic assymetry of the adjacent carbon atom although this is also the situation for the 2-alkyl derivatives. [f] Downfield from internal Me_4Si at 60 MHz.

The n.m.r. spectrum of the prepared compound is consistent with the structure 1-methyl-5-nitro-1,2-dihydroquinoline.

To a stirred solution of 1-methyl-5-nitro-1,2-dihydroquinoline (1 g, 0·0057 mol) and sodium borohydride (0·11 g, 0·003 mol) in tetrahydrofuran (3 ml) under nitrogen, boron trifluoride etherate (0·5 ml) in tetrahydrofuran was added during 25 min. Propionic acid (1 ml) was added and the mixture was boiled under reflux for 1 h. The mixture was washed with sodium hydrogen carbonate solution, the solid products extracted with ether, and recrystallised from ethanol, and had m.p. 58·5—59·5 °C; yield 0·3 g (30%) (Found: C, 62·6; H, 6·3; N, 14·3. Calc. for $C_{10}H_{12}N_2O_2$: C, 62·5; H, 6·3; N, 14·55%); δ (100 MHz; CCl_4) 2·91 (3H, s, NMe), 2·86 (2H, t, 2-H_2), 1·76—2·12 (2H, m. 3-H_2), 3·26 (2H, t, 4-H_2), 6·84—7·22 (2H, m, 6- and 7-H), and 6·58 and 6·66 (1H, 2 × d, 8-H).

1-*Methyl*-6-*nitro*-1,2,3,4-*tetrahydroquinoline*.— *N*-Acetyltetrahydroquinoline (22 g, 0·165 mol) was added to glacial acetic acid (16 g, 0·27 mol) followed by sulphuric acid (98%, 33 ml). The solution was well stirred and cooled in an ice–salt bath. A cold mixture of concentrated nitric acid (8 ml) and concentrated sulphuric acid (3 ml) was added slowly, the temperature being kept below 10 °C. The solution was left at room temperature for 1 h and then it was poured on crushed ice and the organic layer extracted with ether. The ether was removed and the products boiled under reflux with sulphuric acid (70%, 150 ml) for 20 min. The mixture was poured into water and the pH adjusted to *ca.* 1 with dilute (2N) sodium bicarbonate. The precipitate which appeared was filtered off and recrystallised from ethanol giving crystals that were yellow with a blue reflex, m.p. 158—162 °C; yield 10 g (45%) (Found: C, 60·6; H, 5·7; N, 16·0. Calc. for $C_9H_{10}N_2O_2$: C, 60·65; H, 5·65; N, 15·7%); δ ([$^2H_6$]Me_2SO) 7·2—7·5br (1H, s, NH), 2·5—2·8 (2H, m, 2-H_2), 1·6—2·0 (2H, m, 3-H_2), 3·2—3·5 (2H, m, 4-H_2), 7·16—7·9 (2H, m, 5- and 7-H), 6·3—6·6 (1H, d, 8-H). The m.p., analysis, and n.m.r. spectrum [15] indicate that the product is 6-nitro-1,2,3,4-tetrahydroquinoline (lit.,[16] m.p. 161—162 °C).

The solution at pH 1 was neutralised with sodium hydroxide solution and the remaining products filtered off. The mixture was dissolved in benzene and the solution passed down an alumina (Grade IV) column. Two major fractions were observed, the first of which when crystallised consisted of dark red needles, m.p. 70—73 °C, yield 0·55 g (2·5%) (Found: 60·9; H, 5·7; N, 16·0. Calc. for $C_9H_{10}N_2O_2$: C, 60·65; H, 5·65; N, 15·7%); δ ([$^2H_6$]Me_2SO) 8·2—8·6br (1H, s, NH), 2·6—3·0 (2H, m, 2-H_2), 1·6—2·1 (2H, m, 3-H_2), 3·3—3·7 (2H, m, 4-H_2), 7·7—8·0 (1H, d, 6-H), 7·0—7·3 (1H, d, 7-H), and 6·3—6·6 (1H, 2 × d, 8-H). The analysis and n.m.r. spectrum indicate that this compound is 5-nitro-1,2,3,4-tetrahydroquinoline. 6-Nitro-1,2,3,4-tetrahydroquinoline (0·5 g, 0·0028 mol) and trimethyl phosphate (0·12 g, 0·0084 mol) were heated under reflux and after 10 min the mixture was poured into cold water. The solution was made alkaline and the amine extracted with ether. Removal of the ether left a yellow solid which was sublimed at 0·5 mmHg with a bath temperature of 80 °C. The product 1-*methyl*-6-*nitro*-1,2,3,4-*tetrahydroquinoline* is a yellow crystalline solid with a blue reflex, m.p. 88—91 °C; yield 0·26 g (44%) (Found: C, 62·3; H, 6·3; N, 14·3. $C_{10}H_{12}N_2O_2$ requires C, 62·5; H, 6·3; N, 14·55%); δ (CCl_4) 2·95 (3H, s, NMe), 2·6—2·9 (2H, m, 2-H_2), 1·8—2·05 (2H, m, 3-H_2), 3·25—3·5 (2H, m, 4-H_2), 7·5—7·9 (2H, m, 5- and 7-H), and 6·2—6·4 (1H, d, 8-H).

1-*Methyl*-7-*nitro*-1,2,3,4-*tetrahydroquinoline*.—Tetrahydroquinoline (20 g, 0·15 mol) was dissolved in concentrated sulphuric acid (98%; 500 ml) below 5 °C. To this mixture was added a mixture of concentrated nitric acid (15 ml) in concentrated sulphuric acid (98%; 60 ml). The mixture was stirred at below 0 °C for 3 h and then poured on ice (500 g). The solution was neutralised and left overnight after which the resultant precipitate of sodium sulphate and nitration products was filtered off. The organic products were obtained as a red oil after extraction with ether. The red oil was dissolved in an equal volume of ether, and light petroleum (b.p. 40—60 °C) was added until a yellow precipitate started to form. The solution was boiled and more ether (1 ml) added. The product crystallised as yellow needles which were recrystallised from ether–light petroleum (b.p. 40—60 °C) and had m.p. 60—61·5 °C; yield 15·5 g (58%) (Found: C, 60·7; H, 5·6; N, 15·6. Calc. for $C_9H_{10}N_2O_2$: C, 60·65; H, 5·65; N, 15·7%); δ (CCl_4) 4·2—4·5br (1H, s, NH), 2·6—2·9 (2H, m, 2-H_2), 1·6—2·1 (2H, m, 3-H_2), 6·7—7·0 (1H, d, 5-H), and 7·1—7·4 (2H, m, 6- and 8-H). The analysis and n.m.r. spectrum are consistent with the structure 7-nitro-1,2,3,4-tetrahydroquinoline (lit.,[17] m.p. 62—63 °C).

[15] P. J. Black and M. L. Hefferman, *Austral. J. Chem.*, 1964, **17**. 558.

[16] A. L. Mndzhoyan and A. S. Azaryan, *Sintezy Geterotsikl. Soedin., Akad. Nauk Armyan. S.S.R., Inst. Tonkoi org. Khim.*, 1964, 55 (*Chem. Abs.*, 1967, **66**, 55,361).

[17] M. Kulka and R. H. F. Manske, *Canad. J. Chem.*, 1952, **30**, 720.

The mother liquor was evaporated and the red oil obtained dissolved in benzene and passed down an alumina (Grade IV) column. Of the two major fractions thus revealed the first was found to be more of the 7-nitro-1,2,3,4-tetrahydroquinoline. The second fraction crystallised as red needles, m.p. 81—82 °C; yield 0·3 g (1·1%) (Found: C, 60·9; H, 5·3; N, 15·9. Calc. for $C_9H_{10}N_2O_2$: C, 60·65; H, 5·65; N, 15·7%); δ ($CDCl_3$) 4·0—4·5br (1H, s, NH), 2·7—3·1 (2H, m, 2-H_2), 1·7—2·1 (2H, m, 3-H_2), 3·1—3·5 (2H, m, 4-H_2), 6·8—7·2 (2H, m, 5- and 7-H), 6·5—6·7 (1H, 2 × d, 6-H). The m.p., analysis, and n.m.r. spectrum are consistent with the structure 8-*nitro*-1,2,3,4-*tetrahydroquinoline* (lit.,[18] m.p. 82—84 °C).

Methylation of 7-nitro-1,2,3,4-tetrahydroquinoline with trimethyl phosphate gave 1-methyl-7-nitro-1,2,3,4-tetrahydroquinoline as red needles, m.p. 91—92 °C; δ (CCl_4) 2·95 (3H, s, NMe), 2·80 (2H, t, 2-H_2), 1·7—2·2 (2H, m, 3-H_2), 3·25 (2H, t, 4-H_2), 6·85—6·95 (1H, d, 5-H), and 7·2—7·5 (2H, m, 6- and 8-H). For each of the authentic nitrotetrahydroquinolines the n.m.r. absorption pattern for the aromatic protons is distinctive and the assignments given are consistent with the detailed analysis made for a series of nitroquinolines.[15]

Product Analysis.—A typical experiment is described below. This procedure was used for the nitration of both 2-alkyl-1-methyl-1,2,3,4-tetrahydroquinolines and 2-alkyl-1,4-dimethyl-1,2,3,4-tetrahydroquinolines. In each case duplicate experiments were performed. For the largest fraction n.m.r. and u.v. spectra were measured. The n.m.r. absorption pattern for the aromatic protons allowed an unambiguous distinction between 6- and 7-nitro-compounds and the u.v. spectra confirmed this assignment (Table 7).

Analysis of the products of nitration of protonated 2-alkyl-1-methyl-1,2,3,4-tetrahydroquinoline. Potassium nitrate (0·1140 g, 0·0011 mol) in sulphuric acid (82% w/w; 10 ml) was added to 1-methyl-1,2,3,4-tetrahydroquinoline (0·1658 g, 0·0011 mol) in sulphuric acid (82% w/w; 10 ml) and the mixture left for 2 h at 0 °C. The mixture was poured on ice, made alkaline with dilute sodium hydroxide, and the liberated amines were extracted with ether. The ether layer was dried ($MgSO_4$). Following the removal of ether the mixture of nitrated amine was absorbed on alumina (Grade IV) and the column (2 × 30 cm) eluted with a mixture of light petroleum (b.p. 60—80 °C; 20%) and benzene (80%). This procedure separated the largest fraction from the remainder. The solution containing the remainder of the fractions was evaporated almost to dryness, then placed on a silica t.l.c. preparative plate with light petroleum (b.p. 40—60 °C; 80%), benzene (10%), and acetone (10%) as the solvent phase. The amounts of compound isolated from each fraction were expressed as a percentage of the total amount recovered. The total amount of nitro-compounds recovered was in the range 90—98% of the theoretical yield for mononitration.

[18] A. Richardson and E. D. Amstutz, *J. Org. Chem.*, 1960, **25**, 1138; R. Stoermer, *Ber.*, 1898, **31**, 2523.

TABLE 7

U.v. spectroscopic data [a] for *N*-methylnitrotetrahydroquinolines

R at C(4)	R at C(2)	NO_2 substitution	$\lambda_{max.}$/nm	$10^3\varepsilon_{max.}$/ l mol^{-1} cm^{-1}
H	H	7	262	25·58
Me	H	7	262	18·97
H	Me	7	262	44·50
Me	Me	7	261	17·62
H	Et	7	262	46·01
Me	Et	7	261	20·20
H	Pr^i	7	262	47·54
H	Bu^t	7	262	51·96
Me	Bu^t	7	268	19·50
H	Me_2	7	260	20·14
H	H	6	410	29·71
Me	H	6	410	20·62
H	Me	6	410	32·54
Me	Me	6	410	21·35
H	Et	6	410	43·47
Me	Et	6	410	16·90
H	Pr^i	6	410	41·32
H	Bu^t	6	410	
Me	Bu^t	6	410	
H	Me_2	6	410	

[a] Measured in ethanol solution with a Unicam SP 800 instrument.

An experiment designed to test the efficiency of recovery using this procedure and also to confirm that any 5-nitro-product would have been detected is described below.

Recovery of product from an artificial mixture. 1-Methyl-7-nitro-1,2,3,4-tetrahydroquinoline (0·0602 g), 1-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (0·0316 g), and 1-methyl-5-nitro-1,2,3,4-tetrahydroquinoline (0·0062 g) were dissolved in 82% sulphuric acid (30 ml) and the mixture left for 30 min at 0 °C. The mixture was quenched in water and made alkaline with dilute sodium hydroxide. The separation procedure of the previous experiment was followed and the amount of nitro-compounds recovered are shown in Table 8.

TABLE 8

Isomer	Initial amount/g	Amount recovered/g	Recovery (%)
7-Isomer	0·0602	0·0597	99·2
6-Isomer	0·0316	0·0294	93·0
5-Isomer	0·0062	0·0054	87·1
Total	0·0980	0·0945	96·0

Kinetics.—Rate coefficients were measured by the previous method.[1]

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