Amine Oxidation. Part VI.[1] Metal-ion Induced Dehydrative Cyclisation, Reduction, and Reductive Fragmentation of Arylethyldimethylamine N-Oxides

By J. R. Lindsay Smith, R. O. C. Norman,* and A. G. Rowley, Department of Chemistry, The University of York, Heslington, York YO1 5DD

The treatment of 3,4-dimethoxy-NN-dimethylphenethylamine N-oxide with iron(II) ion gives some or all of the following products, depending upon the conditions: the corresponding tertiary and secondary amines, 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline, and 3,4-dimethoxybenzyl alcohol. Factors which govern the course of the reaction (especially the temperature, the concentration of the reagents, and the presence of pyridine) have been examined, and the studies have been extended to the use of titanium(III) in place of iron(II) ion and to the reactions of related N-oxides. The results are consistent with the mediation of an aminium radical cation $ArCH_2$-$CH_2NMe_2^{+\cdot}$ in the formation of each type of product: its one-electron reduction by iron(II) or titanium(III) ion gives the tertiary amine, its one-electron oxidation by iron(III) ion gives secondary amine and (under suitable conditions) the cyclised product, and it undergoes homolysis to the radical $ArCH_2\cdot$ whence non-basic products are derived.

INTEREST in the possibility that tertiary amine N-oxides mediate in the metabolic dealkylation of the parent amines and in the formation of heterocyclic rings during the biogenesis of certain alkaloids has led us to study chemical systems which may serve as models for these processes.[1] We have reported on investigations of two of these systems,[1] namely, the reactions of N-oxides with carboxylic acid anhydrides (Polonovski reaction [2]) and their reactions with sulphur dioxide.[3] The latter proved of particular interest in that the arylethyldimethylamine N-oxide (1a) was found to undergo conversion predominantly into the corresponding secondary amine in aqueous solution but into the tetrahydroisoquinoline (6) in formic acid solution, indicating the

chemical feasibility, at least, of the two biological processes referred to. These two types of model system apparently both involve two-electron steps, and we now report on similar studies in which one-electron changes are involved and radicals mediate. We have used as reagents iron(II) ion, which was the subject of a preliminary communication,[4] and titanium(III) ion, finding that, depending upon the reagent and the conditions, the reactions characteristic of the two-electron reagents [formation of the corresponding secondary and tertiary amines and dehydrative cyclisation of N-oxides such as (1a)] can all be effected, and that there is an additional reaction involving fragmentation of an intermediate aminium radical cation.

[1] Part V, P. A. Bather, J. R. Lindsay Smith, and R. O. C. Norman, J. Chem. Soc. (C), 1971, 3060.

[2] M. Polonovski and M. Polonovski, Compt. rend., 1927, 184, 331; Bull. Soc. chim. France, 1927, 41, 1190.

[3] H. Z. Lecher and W. B. Hardy, J. Amer. Chem. Soc., 1948, 70, 3789.

[4] J. R. Lindsay Smith, R. O. C. Norman, and A. G. Rowley, Chem. Comm., 1970, 1238.

RESULTS AND DISCUSSION

Tertiary amine N-oxides have previously been shown to yield both the parent amines and secondary amines when treated with iron(II) ion, and evidence has been adduced that formation of the latter products involves aminium radical cations and iminium ions analogous to (2) and (4) from arylethyldimethylamine N-oxides, hydrolysis of the latter affording the secondary amine as in Scheme 1.[5,6] When we treated the N-oxide (1a) with iron(II) sulphate in an atmosphere of nitrogen under conditions similar to those employed by Ferris et al.— dilute sulphuric acid under reflux [5,6]—we obtained as the only significant basic product (ca. 50%) the tertiary amine (3a), there being only traces (<1%) of compounds with g.l.c. retention times corresponding to the secondary amine (5a) and the cyclised product (6); the non-basic fraction contained mainly 3,4-dimethoxybenzyl alcohol and some of the corresponding aldehyde, the origin of each of which is discussed later. However, when

clue as to the source of the cyclised product, namely, that it is formed on heating the secondary amine (5a) by the reverse of step (iv), to regenerate the iminium ion (4a), followed by intramolecular electrophilic substitution into the benzenoid ring [step (v)]. This requires only that step (v) has a higher activation energy than step (iv) but, in contrast to the latter, is essentially irreversible. Moreover, the hypothesis is consistent with the results obtained on treating the N-oxide (1a) with sulphur dioxide from which evidence was adduced that the iminium ion (4a) undergoes cyclisation effectively when the solvent is only weakly nucleophilic (formic acid) but does not do so at room temperature when a more strongly nucleophilic solvent (water) is employed. In Scheme 1 the general mechanism of Ferris et al. is modified by indicating the reversibility of step (iv) and elaborated by the inclusion of step (v), for the special case where cyclisation can occur; tests of various aspects of reactions in this Scheme are described in the sequel.

a; Ar = 3,4-(MeO)$_2$C$_6$H$_3$
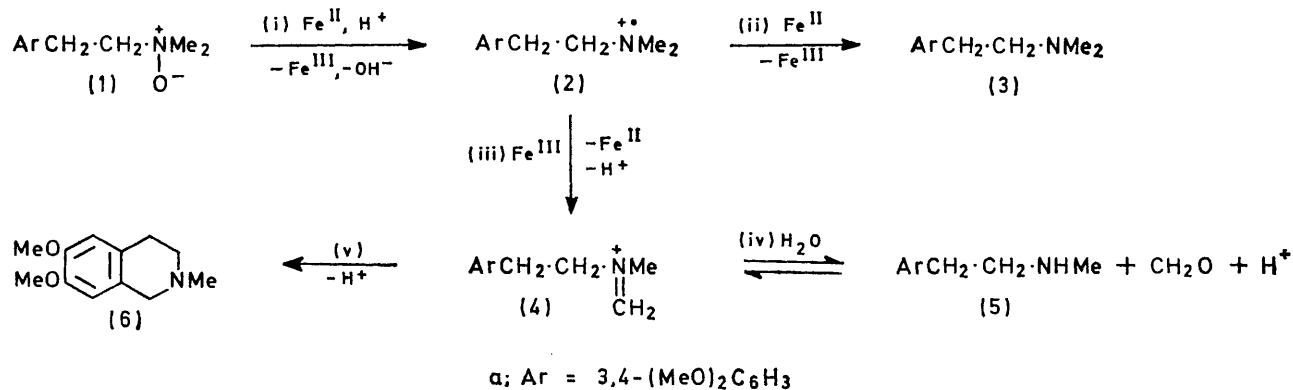
SCHEME 1

enough pyridine was included in the reactants to give pH 5·8, reaction at the reflux temperature for 24 h gave, in addition to 43% of the tertiary amine (3a), 31% of the secondary amine (5a) and 10% of the cyclised product (6). This system was employed for subsequent studies except where stated otherwise.

The initial experiments, in which the reactants were mixed at room temperature and then brought to reflux, were found to have poor reproducibility until it was shown that the reaction temperature is critical; for example, when reaction was conducted at room temperature for 5 days, none of the cyclised product could be detected, and the yields of the tertiary and secondary amine were 58 and 24% respectively. Thereafter, the procedure adopted was to inject an aqueous solution of the N-oxide into the remaining reactants which were already at the reflux temperature; g.l.c. analysis then gave results reproducible to within ±3% of the values quoted.

The marked effect of temperature offered an immediate

First, if the tetrahydroisoquinoline (6) is derived from the secondary amine (5a), then the inclusion of labelled secondary amine in a reaction of unlabelled N-oxide with iron(II) ion should give labelled (6). This proved to be the case; when a sample of the secondary amine in which the N-methyl group was dideuteriated (>95%) was employed, the tetrahydroisoquinoline (6) was found to contain 28 ± 1% of its N-dideuteriomethyl analogue (6; CHD$_2$ for Me).

Secondly, according to Scheme 1, the yield of product (5a) relative to that of (6) should decrease with time; eventually, the yield of the former could, in principle, fall to zero. The data in Table 1 (which also includes the result obtained at room temperature) bear out the first of these predictions [Experiments (2)—(4)]; not only does the ratio of the yields of products (5a) and (6) decrease with time but also, notably, the latter product continues to be formed after 24 h, at which time the N-oxide has been completely removed. However, increase in the reaction time from 70 to 191 h did not

[5] J. P. Ferris, R. D. Gerwe, and G. R. Gapski, J. Amer. Chem. Soc., 1967, 89, 5270.

[6] J. P. Ferris, R. D. Gerwe, and G. R. Gapski, J. Org. Chem., 1968, 33, 3493.

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affect the ratio, possibly because some of the form-aldehyde produced in reaction (iv) is lost by side-re-actions [*e.g.* its oxidation by iron(III) ion; see later] and by evaporation, so that the reverse of reaction (iv) is finally prevented.

TABLE 1

Basic products from reaction of the *N*-oxide (1a) with 0·13M-iron(II) sulphate at the reflux temperature in 0·25M-sulphuric acid containing pyridine (pH 5·8)

		Products (mol %)		
Expt.	*t*/h	(3a)	(5a)	(6)
(1) *	120	58	24	0
(2)	0·5	43	21	0
(3)	24	43	31	10
(4)	70	40	20	20
(5)	191	39	21	20

* At room temperature.

Thirdly, according to Scheme 1, the formation of products (5a) and (6) does not consume iron(II) ion, since the iron(II)–iron(III) conversion in step (i) is reversed in step (iii). In contrast, the formation of 1 mol of the tertiary amine (3a) corresponds to the removal of 2 mol of iron(II) ion. The ratio of the sum of the yields of products (5a) and (6) to the yield of tertiary amine should therefore increase as the initial concentration of iron(II) is reduced. This was found to be so (Table 2). [In experiments (6) and (7), the amounts of iron(II) ion added were not great enough to account for the amount of tertiary amine produced. However, formaldehyde is formed in sufficient amounts in these cases (as estimated by the yields of the secondary amine) to regenerate, in principle, more than the

tertiary amine, to 49%, and a large decrease in the sum of the yields of the products (5a) and (6), to 20%. This is the opposite result of that expected if pyridine were to act only as a Brönsted base because 2,6-lutidine has a somewhat larger pK_a value [7] and should be more effective in catalysing step (iii) and thence the formation of products (5a) and (6). However, 2,6-lutidine is a much weaker (Lewis) base than pyridine towards bulky Lewis acids such as boron trifluoride,[7] and may therefore be expected to complex with iron cations the less readily of the two. Thus, the effectiveness of pyridine at inducing the formation of products (5a) and (6) may be

TABLE 2

Variation in the yields of products from the *N*-oxide (1a) on reaction under the conditions of experiment 3 but with varying concentrations of iron(II) sulphate

		Unchanged	Products (mol %)		
Expt.	Fe^{II}/mM	(1a) (%)	(3a)	(5a)	(6)
(3)	130	0	43	31	10
(6)	6·5	0	17	38	16
(7)	0·65	13	11	47	8

associated, at least in part, with its acting as a ligand for the metal ions and thereby decreasing the relative ease with which iron(II) can reduce, or increasing that with which iron(III) can oxidise, the intermediate (2a). The fact that iron(II)–pyridine complex salts are relatively more stable than simple aqueous iron(II) salts [8] is in accord with this suggestion.

Homolysis of Aminium Radical Cations.—We referred earlier to the formation of the benzylic alcohol (10a) and some of the corresponding aldehyde (12a), as well as the tertiary amine (3a), when the *N*-oxide (1a) reacts with
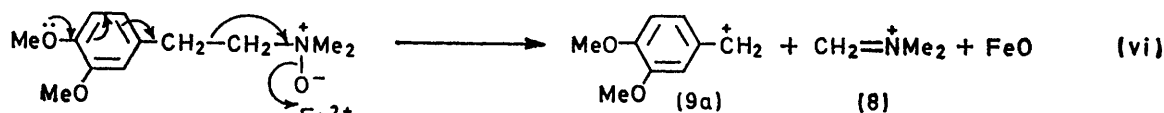
necessary amount of iron(II) by reduction of iron(III); a control experiment showed that this reduction does indeed occur under the reaction conditions. Further, the presence of unchanged *N*-oxide at the end of experiment (7) reflects the slowness of reaction under these conditions and not the total consumption of iron(II) ion; thus, doubling the reaction time reduced the amount of unchanged reactant from 13 to 3%.] More-over, this aspect of the reaction scheme is also consistent with the observation that, for a given initial concentration of iron(II) ion, the ratio of the sum of the yields of products (5a) and (6) to that of (3a) increases during the first 24 h (Table 1); thus, the rate of formation of the former products increases with time, relative to that of the latter, as iron(III) forms at the expense of iron(II) ion.

Finally, we examined the role of pyridine by replacing it with 2,6-lutidine under the conditions of experiment (3). This resulted in a slight increase in the yield of

iron(II) ion in dilute sulphuric acid. The alcohol pre-sumably arises from reaction of the corresponding benzylic carbonium ion (9a) with water, and we con-sidered three ways in which this carbonium ion might be formed. First, the *N*-oxide (1a) could transfer oxygen to iron(II) ion, with concurrent C–C heterolysis, as in reaction (vi); this would be somewhat analogous to the way in which *NN*-dimethyltryptamine *N*-oxide reacts with trifluoroacetic anhydride,[9] and just as in that process C–C heterolysis is facilitated by the +*M* effect of the heterocyclic nitrogen atom,[9] so it would be facilitated in the case of reaction of the *N*-oxide (1a) by the +*M* effect of the 4-methoxy-substituent.

Secondly, the radical cation (2a) could undergo oxidative fragmentation under the influence of iron(III) ion to give the benzylic cation (9a) and the iminium ion (8). Thirdly, β-scission of this radical cation, which has been previously observed for similar species derived from

[7] H. C. Brown, *J. Chem. Soc.*, 1956, 1248.
[8] O. Baudisch and W. H. Hartung, *Inorg. Synth.*, 1939, **1**, 184.

[9] A. Ahond, A. Cavé, C. Kan-Fan, Y. Langlois, and P. Potier, *Chem. Comm.*, 1970, 517.

N-chloroamines,[10] could give the benzylic radical (7a) from which the carbonium ion could be formed by one-electron oxidation by iron(III) ion. If the last path were to occur, other products from the benzylic radical (7a) might be expected, such as the dimer (11a), but although g.l.c. analysis gave a very small peak with the retention time of this dimer, the quantity of the product was too small for its characterisation. However, the essential absence of the dimer does not rule out mediation of the benzylic radical (7a) since iron(III) ion is an effective oxidant for organic radicals [11] and one-electron oxidation in this case should be markedly facilitated by the $+M$ effect of the 4-methoxy substituent [*cf.* the greater ease of one-electron oxidation of the *p*-methoxybenzyl, compared with the benzyl, radical by the titanium(III)–persulphate system [12]]. We therefore, first, replaced the *N*-oxide (1a) by the unsubstituted analogue (1b); the dimer (11b) was obtained in 14% yield, and the products are compared with those from (1a) in Table 3. Secondly, since titanium(IV) ion is a weaker oxidant than iron(III) ion, we employed titanium(III) for reaction with the *N*-oxide (1a); the bibenzyl (11a) was obtained in 5% yield (see also Table 4) and there was no trace of the benzylic alcohol (10a). These results not only confirm mediation of benzylic radicals but also show that, at least for the titanium(III) system which gave none of the benzylic alcohol, neither reaction of the type (vi) nor oxidative fragmentation of the aminium radical cation to the benzylic cation occurs.

TABLE 3

Products from the *N*-oxides (1) with 20mM-iron(II) sulphate for 2 h at the reflux temperature in 0·05M-sulphuric acid

Expt.	*N*-oxide	Unchanged *N*-oxide (%)	Products (mol %)				
			(3)	(5)	(10)	(12)	(11)
(8)	(1a)	25	24	<1	42	2	<1
(9)	(1b)	23	2	9	31	<1	14

Three other aspects of the formation of benzylic products with the use of iron(II) ion were examined. First, our suggested mechanism involves formation of the iminium ion (8), from which dimethylamine and formaldehyde would be expected by hydrolysis in yields comparable with those of products from the benzyl radical. We tested for the presence of formaldehyde by the inclusion in experiment (9) of the secondary amine (5a) with which we know it forms the tetrahydroiso-quinoline (6) on heating; this product was isolated in 40% yield. Secondly, we found that the benzylic alcohol (10a) is oxidised by iron(III) to the corresponding aldehyde (12a), and this no doubt accounts for the formation of the aldehyde in experiment (8). Thirdly, when experiment (8) was carried out for 24 h, the yield of the benzylic alcohol (10a) fell to zero but there was little increase in the yield of the aldehyde. The alcohol is known to undergo self-condensation to give the

trimer (13) on being heated with acid,[13] and this compound was indeed detected in the reaction mixture by t.l.c. and u.v. spectrophotometry. Our conclusions about the mechanism of formation of benzylic products are summarised in Scheme 2.
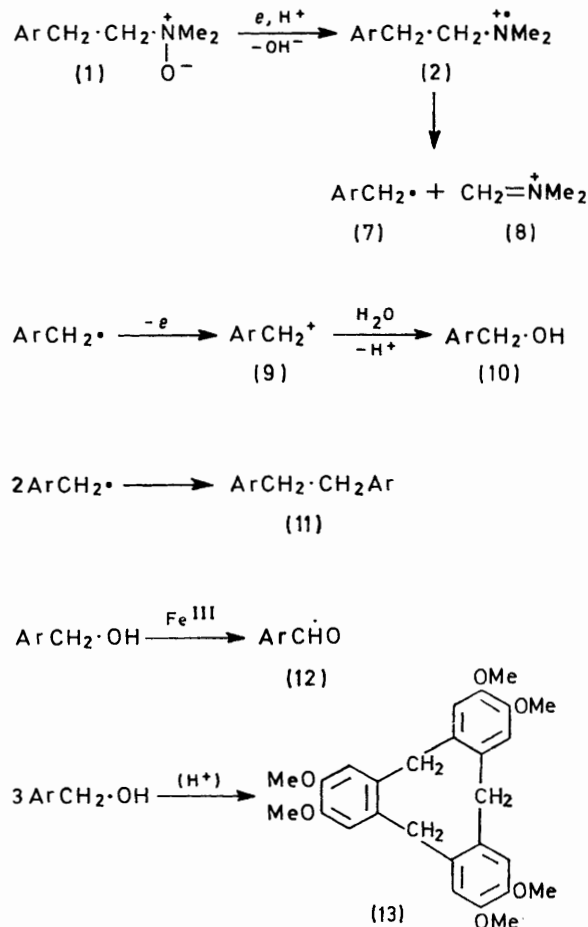
a: Ar = 3.4-(MeO)₂C₆H₃
b: Ar = Ph

SCHEME 2

Finally, we sought information about the factors which determine the relative ease of fragmentation of an aminium radical cation of the type (2) compared with its reduction to the tertiary amine by a given one-electron reducing agent. For this purpose, we chose titanium(III) ion as the reducing agent since we had found that, with the *N*-oxide (1a), the only product from the fragmentation is the dimer (11a) and it was therefore likely that product identification and analysis would be simpler with this system. This proved to be so in that the other arylethyldimethylamine *N*-oxides we examined, except in one instance (see later), gave only dimers of the type (11) from the benzylic species.

[10] F. Minisci and R. Galli, *Tetrahedron Letters*, 1966, 2531.
[11] H. E. De La Mare, J. K. Kochi, and F. F. Rust, *J. Amer. Chem. Soc.*, 1963, **85**, 1437.
[12] R. O. C. Norman and P. M. Storey, *J. Chem. Soc.* (B), 1970, 1099.
[13] A. S. Lindsay, *J. Chem. Soc.*, 1965, 1685. In this paper, formula (IV) should contain a C=O group in place of one CH₂ group.

If formation of the tertiary amine from an N-oxide of the type (1) with titanium(III) ion [14] involves successive one-electron reductions with mediation of the aminium radical cation (2), then the proportion of tertiary amine to the fragmentation product (11) should increase as the rate of addition of titanium(III)-ion solution to a solution of the N-oxide is increased. This was found to be the case; under otherwise identical conditions, the N-oxide (1b) gave 38% of the tertiary amine and 41% of bibenzyl with an addition rate of 0·5 ml min⁻¹ [Table 4, experiment (10)] and yields of these products of 87 and 16%, respectively, when the addition rate was increased to 3 ml min⁻¹. Further, also in accord with expectation, a ten-fold increase in the volume of the solvent for reaction of the N-oxide (1b) under the conditions of experiment (10) caused the yield of bibenzyl to increase to 61% at the expense of the tertiary amine (28%). The ratio of the yields of the two products was also found to be markedly temperature-dependent; reaction under the conditions of experiment (10) but at a lower temperature (60°) gave 94% of the tertiary amine and 5% of bibenzyl, from which we infer that the activation energy for homolytic fragmentation of the aminium radical cation is higher than that for its one-electron reduction by titanium(III) ion.

The effects of substituents in the benzenoid ring of N-oxides of the type (1) in determining the relative ease of reduction and fragmentation of the aminium radical cation are given in Table 4. In addition to the

TABLE 4

Yields of tertiary amine (3) and dimer (11) from N-oxides $3\text{-X-}4\text{-Y-}C_6H_3\cdot CH_2CH_2NMe_2O$ with 0·1M-titanium(III) chloride (added at 0·5 ml min⁻¹) in 0·2M-hydrochloric acid at the reflux temperature

			Products (mol %)	
Expt.	X	Y	(3)	(11)
(10)	H	H	38	41
(11)	OMe	H	42	31
(12)	H	OMe	37	40
(13)	OMe	OMe	89	5
(14)	H	Cl	27	43
(15)	Cl	Cl	15	40

products there quoted, the 3-methoxy-substituted N-oxide gave ca. 14% of a product which was shown by its mass and n.m.r. spectra to be a diphenylmethane with two methoxy and one methyl substituents. It presumably arises by dimerisation of two 3-methoxybenzyl radicals at the methylene group of one and an aromatic carbon of the other followed by a prototropic shift. It was found not to be the compound (14) and was not further investigated.

(14)
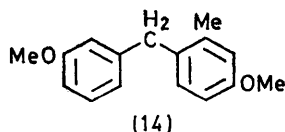
It would be unwise to draw conclusions from the data

[14] R. T. Brooks and P. D. Sternglanz, Analyt. Chem., 1959, 31, 561.

for the 4-chloro- or 3,4-dichloro-substituted compounds since the material accountancy was relatively low; thus, it is possible that products are formed in significant yield in these cases which we did not detect because they are water soluble. However, with the other compounds in the Table the good material balance justifies comment. The introduction of neither a 3- nor a 4-methoxy-substituent into the unsubstituted compound produces a significant effect on the relative ease of reduction and fragmentation of the intervening aminium radical cation. This is not surprising even though a methoxy-substituent can exert a large electronic effect ($+M$) on the reaction of a functional group at the para-position (though not at the meta-position) since, although charged intermediates and transition states are involved, the functional centre is in this case insulated from the benzene ring by two methylene groups. In contrast, the dramatic change produced by a combination of a 3- and a 4-methoxy-substituent is certainly surprising, and it is apparent that a conventional electronic effect (I and M) is not involved. However, an ortho-disposition of two methoxy-groups is very effective at increasing the ease of donation of a π-electron from a benzenoid ring; for example, the absorption frequency for charge-transfer complexes with typical acceptors is lower for o-dimethoxybenzene than for m-dimethoxybenzene and anisole, and the energy of the highest-filled molecular orbital is least for the first of these three.[15] Thus, it is possible that the aminium radical cation (2a) is stabilised, relative to those from the other N-oxides in Table 4, by an intramolecular interaction between the benzenoid ring, as an electron donor, and the nitrogen atom, as acceptor (an interaction which models show to be sterically reasonable), and that this stabilisation serves to retard homolysis of the radical cation more effectively than one-electron reduction.

EXPERIMENTAL

U.v. spectra were determined for solutions in ethanol on a Unicam SP 800 spectrophotometer. ¹H N.m.r. spectra were measured for solutions in deuteriochloroform on a Perkin-Elmer R10 60 MHz spectrometer. Mass spectra were on an A.E.I. MS 12 spectrometer.

Chromatography.—For analytical g.l.c. glass columns (1·6 m × 4·0 mm) were used in a Pye instrument (Series 104, model 24), with a flame-ionisation detector coupled to an RE 511 Georz Servoscribe recorder. The stationary phase was either Celite (80—120 mesh) (B.D.H.) which was treated with 5% KOH and coated with Carbowax 20M (2·5, 10, or 20% w/w, J.J.'s Chromatography Ltd.), or Gas-Chrom Q (100—120 mesh) (Phase Separations Ltd.) coated with the silicones MS 550 (20% w/w, Hopkin and Williams Ltd.) or OV 225 (10 or 1% w/w, Phase Separations Ltd.). Preparative g.l.c. was on a Pye instrument (Series 105), with a glass column (1·6 m × 8·0 mm) packed with diethyleneglycol adipate polyester, LAC-2-R446 (10% w/w, Cambridge Industries Co. Inc., Cambridge, Mass.) on Celite (100—120 mesh) (W. G. Pye and Co. Ltd.). T.l.c.

[15] A. Zweig, J. Phys. Chem., 1963, 67, 506; A. Zweig, J. E. Lehnsen, and A. Murray, J. Amer. Chem. Soc., 1963, 85, 3933.

was on silica gel GF$_{254}$ (Merck) and solid–liquid chromatography was on alumina type H (Laporte Industries Ltd.).

Materials.—Iron(II) sulphate heptahydrate was AnalaR grade and titanium(III) chloride solution (15% w/v) was the low-in-iron laboratory reagent. Nitrogen was British Oxygen white-spot grade and was purified by passage through, successively, chromium(II) chloride solution concentrated sulphuric acid and potassium hydroxide pellets. Commercial samples of phenethylamine, benzyl alcohol, benzaldehyde, 3,4-dimethoxybenzyl alcohol, 3,4-dimethoxybenzaldehyde, and bibenzyl were purified by distillation or recrystallisation.

Arylethyldimethylamines. *NN*-Dimethylphenethylamine was prepared from phenethylamine,[16] and the preparation of its 3,4-dimethoxy-derivative has been described previously.[1] The method for the latter compound was employed to make 4-*methoxy*-NN-*dimethylphenethylamine*, from 4 methoxyphenylacetyl chloride, b.p. 117—120° at 9 mmHg; τ 3·00 (4H, m), 6·31 (3H, s), 7·46 (4H, m), and 7·81 (6H, s); characterised as its *picrate*, m.p. 119—120° (Found: C, 50·3; H, 5·0; N, 13·8. C$_{17}$H$_{20}$N$_4$O$_8$ requires C, 50·0; H, 4·9; N, 13·7%), and the 3-methoxy isomer, b.p. 69—71° at 0·2 mmHg [picrate, m.p. 162—163° (lit.,[17] 162°)]. 4-Chloro-*NN*-dimethylphenethylamine was prepared from 4-chlorobenzyl cyanide with lithium aluminium hydride [18] to give 4-chlorophenethylamine, b.p. 104—105° at 10 mmHg (lit.,[19] 120° at 15 mmHg), followed by methylation as for phenethylamine; it had b.p. 104—105·5° at 10 mmHg [τ 2·80 (4H, m), 7·37 (4H, m), and 7·74 (6H, s)] and was characterised as its *picrate*, m.p. 132—134° (Found: C, 46·6; H, 4·1; N, 13·9. C$_{16}$H$_{17}$ClN$_4$O$_7$ requires C, 46·55; H, 4·15; N, 13·6%). 3,4-*Dichloro*-NN-*dimethylphenethylamine* was prepared from 3,4-dichlorobenzyl chloride by way of [18] 3,4-dichlorophenethylamine [16] and had b.p. 102—105° at 1·5 mmHg, τ 2·70 (3H, m), 7·38 (4H, m), and 7·75 (6H, s). It was characterised as the *picrate*, m.p. 195—197° (Found: C, 43·35; H, 3·8; N, 12·5. C$_{16}$H$_{16}$Cl$_2$N$_4$O$_7$ requires C, 43·0; H, 3·6; N, 12·5%).

Arylethylmethylamines. The preparation of 3,4-dimethoxy-*N*-methylphenethylamine has been described.[1] *N*-Methylphenethylamine was prepared by converting phenethylamine into its *N*-formyl derivative by the method of Mandel and Hill [20] followed by reduction with lithium aluminium hydride; [21] it had b.p. 90—91° at 12 mmHg (lit.,[22] 91—93° at 18 mmHg). 3,4-Dimethoxy-*NN*-dideuteriomethylphenethylamine was prepared from 3,4-dimethoxyphenethylamine by *N*-formylation followed by reduction with lithium aluminium deuteride; mass spectral analysis showed the product to be >95% dideuteriated.

Bibenzyls. 3,3′,4,4′-Tetramethoxybibenzyl, prepared from condensation of 3,4-dimethoxyphenylacetyl chloride with *o*-dimethoxybenzene [23] followed by reduction,[24] had m.p. 105—106° (lit.,[25] 108—109°), τ 3·3 (6H, m), 6·20 (12H, s), and 7·20 (4H, s). The following procedure was used for

three other bibenzyls. The benzyl halide (0·1 mol) in sodium-dried ether (70 ml) was added slowly with stirring to magnesium turnings (0·1 mol) in dry ether (30 ml) in an atmosphere of nitrogen. When all the magnesium had dissolved, small pieces of lithium (0·1 mol) were added, followed by more benzyl halide (0·1 mol). The mixture was heated under reflux in an atmosphere of nitrogen for 20 h and to the ice-cooled mixture, water (10 ml) and then 2M-hydrochloric acid (10 ml) were added. When the reaction had subsided, water (150 ml) was added and the mixture was stirred until any excess of lithium had dissolved.

The ether layer was removed and the aqueous layer was extracted with ether (100 ml). The combined ether extracts were dried (MgSO$_4$) and distilled, to leave the bibenzyl. 3,3′-Dimethoxybibenzyl had b.p. 190—192° at 9 mmHg (lit.,[26] 195—200° at 10 mmHg), 4,4′-dichlorobibenzyl had m.p. 94—96° (lit.,[27] 102°), and 3,3′,4,4′-tetrachlorobibenzyl had m.p. 110—112° (lit.,[28] 111—112°).

N-Oxides. Preparation and estimation were by the procedures described previously for 3,4-dimethoxy-*NN*-dimethylphenethylamine *N*-oxide [1] and the materials were characterised as their picrates (Table 5).

Aryl group	M.p.	Analysis (%)					
		Found			Requires		
		C	H	N	C	H	N
Phenyl	145—146·5°	48·8	4·6	14·3	48·7	4·6	14·2
3-Methoxyphenyl	106—108	48·2	4·7	13·4	48·1	4·75	13·2
4-Methoxyphenyl	99—100	48·1	4·65	13·1	48·1	4·75	13·2
4-Chlorophenyl	135—137	45·0	4·0	13·1	44·8	4·0	13·1
3,4-Dichlorophenyl	155—157	41·4	3·4	12·0	41·5	3·5	12·1

10,15-Dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo-[*a,d,g*]cyclononene (13), prepared by heating 3,4-dimethoxybenzyl alcohol (1 g) with 0·25M-sulphuric acid under reflux for 1·5 h and recrystallising the precipitate from ethanol-light petroleum (b.p. 60—80°), had m.p. 231—232° (lit.,[13] 234°).

2-*Methyl*-3′,4-*dimethoxydiphenylmethane* was prepared by Friedel–Crafts reaction between 3-methoxybenzoyl chloride and 3-methoxytoluene, following the method of Vogel,[29] and reduction of the resulting ketone by the procedure of Nystrom and Berger; [30] it had b.p. 196—198° at 10 mmHg, and a small sample was isolated by preparative g.l.c. for microanalysis; τ 2·83—3·37 (7H, m), 6·13 (2H, s), 6·28 (3H, s), 6·30 (3H, s), and 7·81 (3H, s); *m*/*e* 242 *M*$^+$, 100%, 227 (31), 211 (11), 138 (28), 135 (26), 121 (22), 109 (18), 91 (12), and 77 (18), *m** 212·9 (242 ⟶ 227) (Found: C, 79·5; H, 7·5. C$_{16}$H$_{18}$O$_2$ requires C, 79·3; H, 7·5%).

Reactions of N-Oxides.—(i) 3,4-*Dimethoxy*-NN-*dimethylphenethylamine*-N-*oxide with iron*(II) *ion in the presence of a*

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base. Iron(II) sulphate heptahydrate was dissolved in 0·28M-sulphuric acid (45 ml) and the pH of the solution was adjusted to 5·8 by addition of pyridine or other base. The clear green solution was purged with nitrogen and heated to the reflux temperature under nitrogen; a solution of the *N*-oxide (2·5 mmol) in water (*ca.* 5 ml) was then injected into it. The mixture rapidly darkened and a brown precipitate formed. After the desired reaction time the mixture was cooled, acidified with sulphuric acid to pH 1, and extracted with ether (4 × 100 ml). The aqueous residue was made strongly alkaline with potassium hydroxide and extracted with ether (4 × 100 ml). The ether solutions were dried (MgSO₄) and evaporated before analysis by g.l.c.

The aqueous solution was acidified with sulphuric acid and unchanged *N*-oxide was determined by the following procedure. The *N*-oxide was reduced with titanium(III) chloride, the solution was made strongly alkaline, and the liberated tertiary amine was extracted into ether and analysed by g.l.c.

The procedure used for the experiment in the presence of 3,4-dimethoxy-*NN*-dideuteriomethylphenethylamine was that described above with the addition of the isotopically labelled secondary amine (0·17 g). The deuterium content of the *N*-methyltetrahydroisoquinoline was measured by combined g.l.c.–mass spectrometry.

(ii) NN-*Dimethylphenethylamine* N-*oxide and its* 3,4-*dimethoxy-derivative with iron*(II) *ion in the absence of a base.* The *N*-oxide (1 mmol) in water (*ca.* 5 ml) was added to a solution of iron(II) sulphate in 0·05M-sulphuric acid (50 ml). The mixture was purged with nitrogen for 30 min and heated to reflux under nitrogen. The effluent nitrogen from the reaction of *NN*-dimethylphenethylamine *N*-oxide was passed through ether (100 ml), which was cooled with

acetone–solid carbon dioxide, to trap bibenzyl. The analytical procedure was that described above. The same procedure was used for reaction in the presence of 3,4-dimethoxy-*N*-methylphenethylamine (0·15 g).

For experiments aimed at the detection of 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a,d,g*]cyclononene (**13**), the reaction mixture was extracted with dichloromethane and the concentrated extract was analysed by t.l.c. with chloroform–light petroleum (b.p. 60—80°). The R_F value and u.v. spectrum of material eluted from the t.l.c. plate were identical to those of the authentic compound.

(iii) *The* N-*oxides with titanium*(III) *chloride solution.* The *N*-oxide (1 mmol) in water (*ca.* 5 ml) was added to 0·2M-hydrochloric acid (25 ml), and the solution was purged with nitrogen and heated to reflux under nitrogen. A solution of 0·1M-titanium(III) chloride (50 ml), which had previously been deoxygenated, was added at a controlled rate to this solution. The addition was halted when the *N*-oxide had been consumed [as judged by persistence of the colour of the titanium(III) ion in the reaction mixture]. The extraction and analysis were similar to those described above, except that the initial extraction from the acid solution was with dichloromethane.

An unknown product from the reaction of 3-methoxy-*NN*-dimethylphenethylamine *N*-oxide thought to be a methyldimethoxydiphenylmethane was isolated from the reaction mixture by preparative g.l.c. and had τ 2·9—3·4 (7H, m), 6·10 (2H, s), 6·21 (3H, s), 6·24 (3H, s), and 7·69 (3H, s); *m/e* 242 *M*⁺, 100%, 227 (21), 211 (16), 165 (11), 135 (6), 122 (22), 121 (44), and 91 (14).