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ACID-CATALYZED OXYGEN-TRANSFER REACTIONS OF *ORTHO*-ALKENYLDIMETHYLBENZYLAMINE OXIDES

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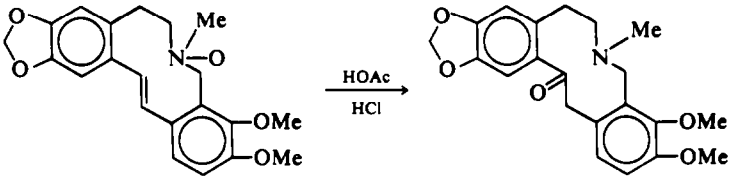
Abstract—Several *ortho*-alkenyldimethylbenzylamine oxides were found to rearrange in strong acid media to mixtures of aminophthalans and conjugated aminoketones.

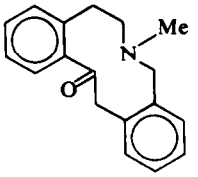
Tertiary amine oxides are most accurately represented as $R_3N^+O^-$ with formal charges residing on both the electron-deficient nitrogen and the electron-rich oxygen. These compounds have attracted considerable attention in recent years because of their tendency to undergo a wide variety of rearrangements[1] and their postulated importance as metabolic intermediates in biological systems.[1a,2]

In the course of their studies on the interconversion of the protoberbine and protopine alkaloids, Haworth and Perkin[3] observed that amine oxide **1** isomerized to allocryptopine (**2**) when heated with a mixture of acetic and hydrochloric acids. This reaction was then utilized to prepare the protopine alkaloids cryptopine, protopine, and cryptopalmatine.[3,4]



1 **2**

More recently it has been used by Giacopello and Deulofeu[5] to prepare the alkaloids fagarine, hunennamanine, and muramine (identical to cryptopalmatine) as well as the simple unsubstituted compound **3**. The latter was much less reactive toward rearrangement than the alkaloid systems which all bear methoxy and/or methylenedioxy substituents on both aromatic rings.



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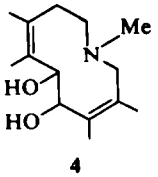

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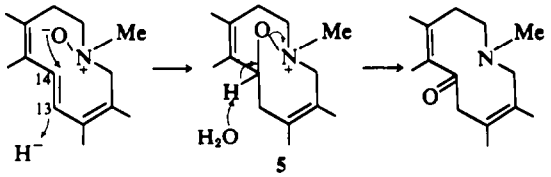
There are only two references in the literature concerning the mechanism of this reaction. In 1954 Manske[6] suggested vicinal diol **4** as an intermediate. Russell[7] tested this hypothesis and found it to be untenable. He proposed an alternate mechanism involving nucleophilic attack of the oxide oxygen on C_{14} with protonation at C_{13} leading to bridged species **5**. Loss of the C_{14}-hydrogen via a Hofmann type biomolecular cleavage provides the product:



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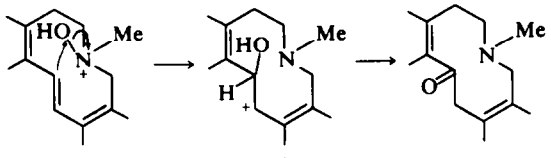
A third mechanism may be written where the olefinic bond nucleophilically attacks the protonated oxide function analogous to the epoxidation of an olefin. The resultant intermediate (**6**) then loses a proton and tautomerizes to product:



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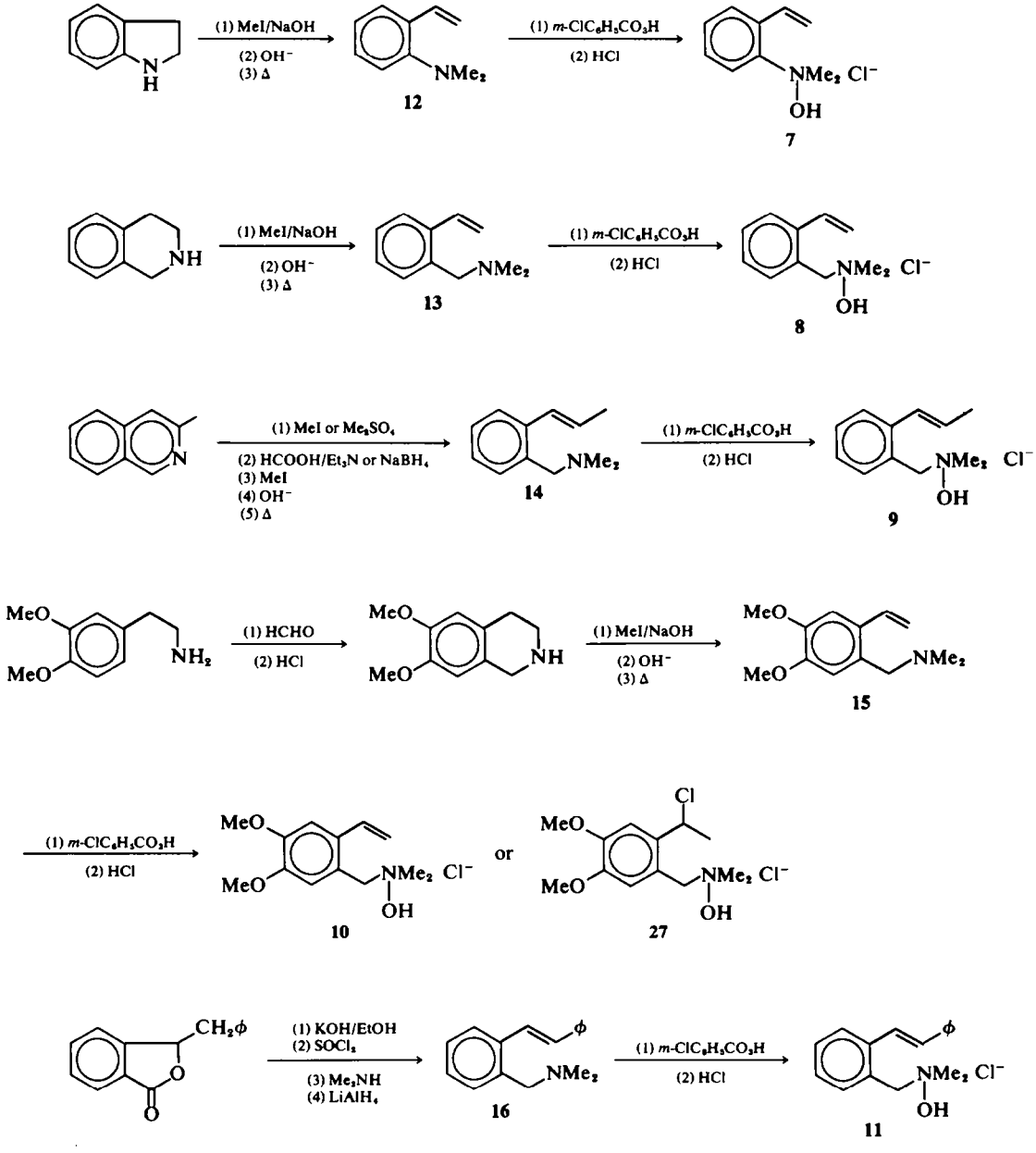
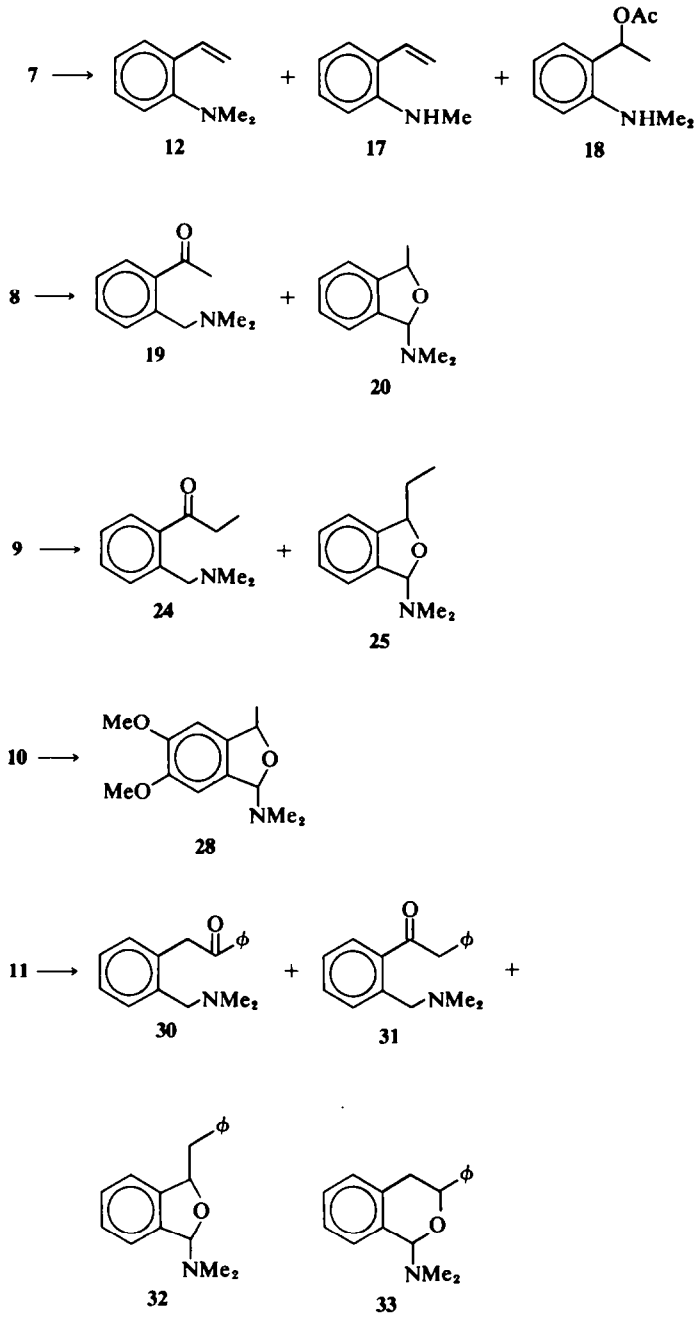
We were interested in determining if this O-transfer reaction could be effected in simpler systems so as to make it more amenable for study.

Four model compounds were prepared (**7**, **8**, **9**, **10**) which incorporate the N_7 through C_{14} segment of the alkaloid system and one (**11**) which contains all but one carbon of the berberine skeleton. All are *ortho*-alkenyldimethylaniline- or dimethylbenzylamine oxides with the olefinic and N-oxide functions in close proximity but, lacking the ten-membered ring of the alkaloid system, should be considerably less rigid.

The synthetic routes to these compounds are outlined in Scheme 1. The vinyl amines **12**, **13**, **14**, and **15** were prepared by Hofmann degradation of the quaternary metho-salts of the appropriate cyclic precursors, while **16** was prepared from a known *ortho*-substituted stilbene. The N-oxides were prepared by direct oxidation of the vinylamines with *meta*-chloroperbenzoic acid.[8] This oxidation was exceeding clean and facile to carry out. All N-oxides were converted to the hydrochloride salts and purified by repeated recrystallization. The salts were used directly in the rearrangement studies; the results are summarized in Scheme 2.



SCHEME 1



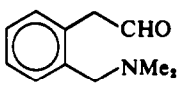
SCHEME 2

The choice of 2-vinyl-N,N-dimethylaniline oxide hydrochloride (**7**) as the first compound to study was an unfortunate one. When this compound was heated at 120–130° in mixtures of glacial acetic acid and either 12 M hydrochloric acid or anhydrous hydrogen chloride for 24–30 hr, dark, gummy complex mixtures were formed. Shorter reaction times and lower temperatures resulted in considerable recovery of starting material. The products which were identified from this reaction are shown in Scheme 2. Vinyl amine **12** arises from deoxygenation of the N-oxide and amine **17** probably via a Polonovski-type demethylation. Simple addition of acetic acid across the double bond gives rise to **18**. No aldehyde or ketone corresponding to oxygen transfer to the vinyl group were found. When

amine **12** itself was subjected to the reaction conditions, the same product mixture was obtained in somewhat better yields.

2-Vinyl-N,N-dimethylbenzylamine oxide hydrochloride (**8**), a compound more closely related to the alkaloid systems, did undergo O-transfer to give ketone **19**, readily identified by analytical and spectral data (see Experimental Section). None of the isomeric aldehyde (**21**) corresponding to O-transfer to the terminal vinyl carbon was detected. The major product was phthalan **20** isolated as an inseparable mixture of geometrical isomers. Its structure was verified by spectral data and chemical transformations to known compounds (Scheme 3).

In the NMR the CH_3—CH— protons of **20** appear as a doublet and a multiplet at 1·47 and 5·21 δ respectively, the second methine proton as a sharp multiplet at 5·95δ, the N-methyls as a singlet at 2·28δ, and the aromatic protons at 7·10δ. Both methine signals display coupling more complex than simple first order. This can arise either from long range coupling of the two methine protons across the ring, as is observed with phthalan **22**[9], or from an unequal mixture of *cis* and *trans* isomers with slightly different chemical shifts. Both effects seem to be present here. Attempts to decouple the methine protons simplified the spectrum slightly but did not give a first order pattern.



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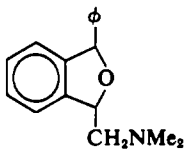

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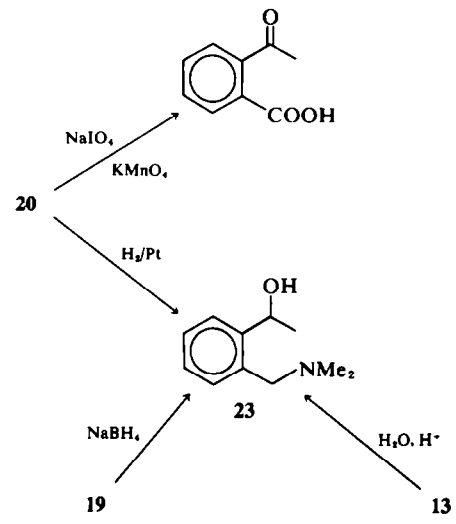
Lemieux oxidation of **20** afforded 2-acetylbenzoic acid, and catalytic hydrogenation afforded amino alcohol **23**. This same alcohol was obtained when ketone **19** was chemically reduced or when vinyl amine **13** was hydrated.

Alcohol **23** exhibited intramolecular H-bonding as evidenced by IR dilution studies and the nonequivalence of the methylene protons in the NMR, where they appeared as a symmetrical AX quartet (J = 12 Hz). Simple hindered rotation due to steric interaction of the *ortho*-groups may also contribute to the nonequivalency of these protons as the acetate of **23** displayed the same AX pattern in the NMR even though it is incapable of H-bonding.

Vinyl amine **13** under the reaction conditions added water and acetic acid to give alcohol **23** and its acetate ester. No ketone (**19**) or phthalan (**20**) were formed. Ketone **19** was stable to the reaction conditions, but phthalan **20** was not. The products formed from **20** were not identified, but they appeared to be no longer monomeric. There is no interconversion between **19** and **20** under the reaction conditions demonstrating that they are formed by



SCHEME 3

two independent, essentially irreversible pathways.

The combined yield of **19** and **20** ranged from 51–63%, and the relative proportion of each varied with the reaction conditions. With 2:1 acetic acid-hydrochloric acid (12 M) mixtures, **20** comprised 76–85% of the volatile product mixture while **13** accounted for 15–24%. With 12 M hydrochloric acid alone, the relative yield of ketone increased to 35% with an increase in total overall yield as well so that the higher proportion of ketone cannot be attributed to increased decomposition of **20**. With acetic acid alone, neither product was formed, and with dilute hydrochloric acid (0·12 M), prolonged heating was necessary to achieve low yields (12%) of products with much recovered N-oxide. These results indicate that a high concentration of strong acid is necessary for O-transfer to occur.

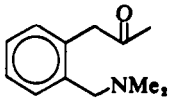
2-(1-Propenyl)-N,N-dimethylbenzylamine oxide hydrochloride (**9**) behaved analogously to oxide salt **8** giving rise to 30–50% yields of a mixture of ketone **24** and phthalan **25** and no detectable quantity of the isomeric ketone (**26**). The proportions of phthalan to ketone again varied with reaction conditions ranging from 63:27 in 2:1 AcOH–HCl (12 M) to 97:3 in 1·2 M HCl alone, but decreased acid concentration inhibited the formation of both products. Heating the oxide hydrochloride in acetic acid saturated with anhydrous hydrogen chloride produced several unidentified materials in low yield but none of the usual products indicating the necessity of the presence of a good nucleophilic solvent such as water.

Phthalan **25** in the NMR clearly showed the presence of *cis* and *trans* isomers. The side chain methyl group exhibited an unsymmetrical quartet (J = 7 Hz) arising from two overlapping triplets of differing intensities and chemical shifts, while the N-methyl groups of the two isomers were non-

equivalent and displayed two sharp singlets of different heights separated by 3 Hz. The methylene and adjacent methine signals were complex multiplets, and the lower field methine was also slightly broadened.

The methoxy-substituted compound, 2-vinyl-4,5-dimethoxy-N,N-dimethylbenzylamine oxide hydrochloride (**10**), as expected, exhibited exceptional reactivity. The N-oxide was first isolated as a stable *meta*-chlorobenzoate salt. Treatment of this salt in methylene chloride with hydrogen chloride afforded either of two products depending on the quantity of acid used. With a slight excess of hydrogen chloride at 0°, the expected vinylic N-oxide salt (**10**) was obtained. With a large excess of acid, also at 0°, addition to the vinyl system occurred affording a compound identified as the hydrochloride salt **27** (Scheme 1). This material was very reactive and appeared to undergo spontaneous loss of hydrogen chloride.

Both chloride salts (**10** and **27**) and the meta-chlorobenzoate salt rearranged in 12 M HCl to identical product mixtures at a much faster rate than the other oxide hydrochlorides studied. Only one product was formed in yields sufficient for identification, and this proved to be phthalan **28**. This material was difficult to purify as it decomposed both on VPC and column or TLC, and it was never obtained in a completely pure state. No evidence for the presence of conjugated ketone **29** in the mixture was found.



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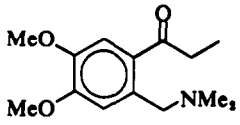

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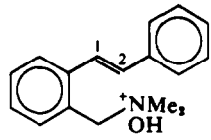
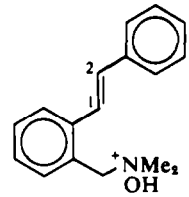
The final compound studied was 2-styryl-N,N-dimethylbenzylamine oxide hydrochloride (**11**). With this compound, both predicted ketone products are conjugated so that the two sites for O-transfer should be essentially equivalent on electronic grounds. Upon treatment with refluxing 12 M HCl, **11** gave a complex mixture of products containing one major and three minor components, which were resolved with varying degrees of success by VPC. The major component comprised 56–75% of the total volatile product and was identified as 2-(N,N-dimethylaminomethyl)benzyl phenyl ketone (**30**) by independent synthesis.[10] Although not obtained completely pure, the minor component immediately preceding **30** on the VPC column displayed spectral characteristics agreeing very well with the isomeric ketone, benzyl 2-(N,N-dimethylaminomethyl)phenyl ketone (**31**).[11] A second minor component corresponded most closely in spectral data to phthalan **32** (Experimental), but the isochroman isomer **33** could not be rigorously excluded. The fourth minor component was not identified. It was produced in very small amounts and decomposed on storage.

A study of the product mixture composition *vs* time of this reaction showed that the concentration of phthalan **32** reached a maximum early in the reactioh (15 hr) then gradually decreased to only trace amounts (64 hr). The unknown minor component also disappeared as the reaction progressed. The ratio of ketone **30** to **31** appeared to be approaching a constant value after 45–64 hr, with **31** being formed more slowly than **30**.

Examination of a model of **11** shows that the steric effects operative in the alkaloid system can also apply here. Assuming the molecule retains the *trans*-stilbene configuration, rotation about the Ar—C_1 bond results in two conformations, **11a** and **11b**. In conformation **11a** the N-oxide oxygen can lie directly above the π-bond at C_2 leading to **30**. Approach to C_1, leading to **31**, is not as close but should still result in sufficient overlap to allow bonding. In conformation **11b**, C_1 retains its position within interacting distance, while C_2 does not. However, interconversion between these two conformations should be rapid, and this predicts that **30** will be the preferred product, which is what is observed.



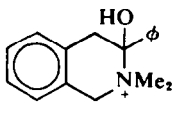
11a



11b

In addition to the volatile product mixture, which was produced in 20–40% yields, a salt was recovered from the aqueous layers which seems to be a quaternary ammonium compound. It undergoes no change when treated with either acid or base thus rendering structures such as **34–37** doubtful. Its identity has not yet been established.

The vinylbenzylamine oxides appear to be, at



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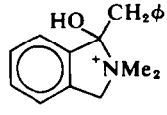

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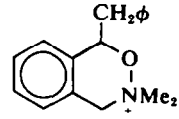

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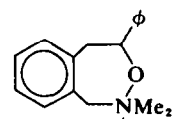

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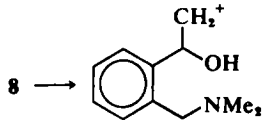
best, fair models for the rearrangement of Haworth and Perkin. Analogous ketone products are produced, but the preferred reaction pathway is that leading to phthalans. Preliminary attempts to induce oxygen transfer intermolecularly (*i.e.*, with styrene or cyclohexene and N,N-dimethylbenzylamine oxide) have been completely unsuccessful.[12]

Several mechanisms may be written for the formation of ketone and phthalan products in these reactions, but in the absence of additional data, it is impossible to choose among them. However, the mechanism involving nucleophilic attack of the double bond on the protonated oxide function (see intermediate **6**) does appear to be ruled out. Such a mechanism, in the case of **8**, would lead to an unstabilized primary carbonium ion (**40**).



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EXPERIMENTAL

M.ps are uncorrected. IR spectra were run on Perkin-Elmer Infracord and Model 337 spectrophotometers. UV spectra were measured on a Perkin-Elmer Model 202 spectrophotometer. NMR spectra were taken at 60 MHz on a Jeolco Model C60-H instrument by S. Baniukiewicz and C. Hsieh with tetramethylsilane as an internal standard. VPC was done with a Varian-Aerograph Model A90-P3 with the following columns: Column A—3% SE-30, 60/80 Chrom W, 10′ × 3/8″; column B—10% QF-1, 60/80 Chrom W, a/w DMCS, 10′ × 1/4″; column C—20% QF-1, 60/80 Chrom W, a/w DMCS, 10′ × 1/4″; column D—3% UCON HB 5100, 60/80 Chrom G, 10′ × 1/4″; column E—10% UCON 50 LB 550 X, 70/80 Anakrom ABS, 10′ × 1/4″. Microanalyses were performed by M-H-W Laboratories, Garden City, Michigan, Galbraith Laboratories, Knoxville, Tennessee, and Atlantic Microlab, Atlanta, Georgia.

2-Vinyl-N,N-dimethylaniline (**12**). N,N-Dimethylindolinium iodide was prepared by slow addition of MeI (42·6 g; 0·30 mol) to a soln of NaOH (4·8 g; 0·12 mol) in 50 ml water and indoline (14·3 g; 0·12 mol) at 0°. The mixture was warmed to 25° and then refluxed 1·5 hr. The aqueous soln was placed in a separatory funnel, the excess MeI was drained, and the mixture was extracted with chloroform. About 12 ml MeOH was added to the extract to insure complete soln, and it was then dried over $MgSO_4$, filtered and evaporated to 23·5 g (71%) crude methiodide. Decolorization with Norit and crystallization from MeOH afforded 22·8 g colorless material, m.p. 195–6° dec (lit[13] 196–7° dec). Upon standing overnight the original aqueous soln deposited an additional 5 g of product (total yield 81%).

The methiodide (25·0 g; 0·09 mol) was dissolved in 500 ml water and was passed through a column containing 75 g Rexyn 201(OH) ion-exchange resin which had been washed with water until neutral. The quaternary hydroxide salt was eluted with water (1·0–1·5 l) which was then removed by evaporation at reduced pressure to give a viscous oil. This oil was subjected to vacuum distillation at 4 mm. Residual water distilled at 29° and the product (**12**) at 66° (3 mm). The two phase distillate was extracted with ether, dried with $MgSO_4$, and the ether removed at reduced pressure. The product was redistilled to give 9·0 g (66%) colorless liquid, b.p. 85° (10 mm) [lit[13] 78–80° (3 mm)].

The hydrochloride displayed m.p. 155–6° dec (methanol/acetone); IR (nujol) 2290, 1610, 927, 769 cm^{-1}; NMR ($CDCl_3$) τ 6·68 (s, 6H), 4·05–4·45 (unsym. q, 2H), 1·86–2·70 (m, 4H); NMR (D_2O) τ 6·66 (s, 6H), 3·34–4·35 (unsym. q, further split, 2H), 2·65–3·12 (unsym. q, 1H), 2·30–2·50 (m, 4H).

2-Vinyl-N,N-dimethylaniline oxide hydrochloride (**7**). To **12** (1 g; 0·007 mol) in 10 ml methylene chloride was added dropwise with stirring 85% *m*-chloroperbenzoic acid (1·38 g; 0·007 mol) in 30 ml methylene chloride. The mixture was stirred at 25° for 2 hr, and then the soln was evaporated to a viscous oil which could not be crystallized. The oil was dissolved in 10 ml acetone and was treated with anhyd HCl for 10 min at 0°. The soln became pink and gradually precipitated a solid. Precipitation was completed by diluting the soln with anhyd ether which yielded 1·2 g (88%) pale pink solid, m.p. 163–4° dec. The product was dissolved in a mixture of MeOH and acetone and reprecipitated with ether giving 0·99 g (74%) white crystals, m.p. 164–6° dec; IR (nujol) 2340, 1608, 961, 942, 767 cm^{-1}; UV (C_2H_5OH) λ_{max} 211, 238, 275 (infl) mμ; NMR (D_2O)τ 5·95 (s, 6H), 4·08–4·49 (d of unsym. d, 2H), 2·00–2·75 (m, 4H). (Found: C, 59·94; H, 6·99; N, 7·01. Calcd for $C_{10}H_{14}NOCl$: C, 60·14; H, 7·07; N, 7·01.)

2-Vinyl-N,N-dimethylbenzylamine (**13**). N,N-Dimethyltetrahydroisoquinolinium iodide was prepared from freshly distilled tetrahydroisoquinoline (20·6 g; 0·155 mol) and MeI (25 ml; 0·40 mol) in the manner described above. The pale yellow crystals (44 g, 86%), m.p. 185–9°, dec, were purified by recrystallization from MeOH to m.p. 189-91° dec (lit[14] 192°, 189°).

The methiodide was converted to the hydroxide by passage through a column of Rexyn 201(OH). The hydroxide was then pyrolyzed as described for **12** to give, after extraction and distillation, 6·42 g (66%) **13**, b.p. 65° (5–6 mm) [lit[15] 102° (1–2 mm)].

The hydrochloride displayed m.p. 169–170°; IR (nujol) 2630, 1625, 1020–984, 943–920, 780, 740 cm^{-1}; NMR (D_2O) τ 6·50 (s, 6H), 5·18 (s, 2H), 3·95-4·55 (unsym. q, further split, 2H), 2·55–3·05 (unsym. q, 1H), 2·15–2·55 (m, 4H).

2-Vinyl-N,N-dimethylbenzylamine oxide hydrochloride (**8**). This material was prepared in the same manner as **7**. It displayed m.p. 141–4° dec; IR (nujol) 2605, 1610, 997, 916, 884, 780, 725 cm^{-1}; NMR (D_2O) τ 7·14 (s, 6H), 5·58 (s, 2H), 3·95–4·60 (q of d, 2H), 2·65–3·17 (unsym. q, 1H), 2·20–2·65 (m, 4H). (Found: C, 61·71; H, 7·67; N, 6·59. Calcd for $C_{11}H_{16}NOCl$: C, 61·82; H, 7·55; N, 6·55.)

2,3-Dimethyl-11,2,3,4-tetrahydroisoquiniline

A. Formic acid/triethylamine method.[16] To 3-methylisoquiniline (27·2 g; 0·020 mol) in a 250 ml flask equipped with a condenser, Me_2SO_4 (25·2 g; 19·0 ml, 0·02 mol) was added in portions through the condenser. After the reaction had subsided, the mixture was heated on a steam bath for 30 min until it had completely solidified. The mass was dissolved in 200 ml boiling EtOH, placed in ice and diluted with cold EtOAc until a thick white ppt formed. Filtration gave 30 g tan solid. The filtrate was concentrated and diluted with ether several times to yield 20 g more. The total yield of 3-methylisoquiniline methosulfate was 49·2 g (93%), m.p. 142–5°. Because of its hygroscopic nature, it

was not purified further but was dissolved in 122 ml formic acid, and to this was added slowly 112 ml triethylamine. A vigorous reaction ensued. The mixture was then refluxed for 3 hr. It was cooled, basified with Na_2CO_3 and extracted with ether. The ether extract was washed with a large volume of water to remove most of the triethylamine then dried over $MgSO_4$ and concentrated to 26 g pale green liquid. The remaining ether and amine were removed by distillation, and the residue was distilled to give 20·1 g (63% overall) of product, b.p. 63° (0·15 mm), $n_D^{22.5}$ 1·5360 (lit[17] n_D^{25} 1·5331).

B. Sodium borohydride method.[18] MeI (10 ml) 3-methylisoquiniline (14·3 g) and 100 ml anhyd ether were combined and refluxed several hr. The methiodide (20·7 g) was removed by filtration and was washed with ether to give m.p. 222–30° dec (lit[19] 219°). The filtrate was warmed overnight with excess MeI yielding 6·2 g more of m.p. 222–7° dec for a total yield of 26·9 g (95%).

A suspension of 26·2 g of the methiodide in 130 ml water cooled in an ice bath was treated with 5 g $NaBH_4$ portion-wise with stirring. Considerable foaming occurred, and the salt gradually dissolved, followed by formation of a yellow oil within a few min. The mixture was stirred for 35 min in ice then extracted with ether. The extracts were washed with water, dried ($MgSO_4$) and concentrated. Vacuum distillation yielded 9·1 g (57% overall) of the product, b.p. 65° (0·55 mm). A second fraction, b.p. 111°, appeared to be an amine-borane complex.

2-(1-*Propenyl*)-N, N-*dimethylbenzylamine* (**14**). 2, 2, 3-Trimethyl-1, 2, 3, 4-tetrahydroisoquinolinium iodide was prepared from 2, 2-dimethyl-1, 2, 3, 4-tetrahydroisoquiniline (9·1 g; 0·057 mol) and MeI (9·1 g; 0·064 mol) in 92% yield, m.p. 207–209° dec. It was converted to the hydroxide by passage through a Rexyn 201(OH) ion-exchange column and pyrolyzed. The product (**14**) was redistilled to give 4·42 g (58%), b.p. 68° (0·3 mm); $n_D^{22.5}$ 1·5377; IR (neat) 1650, 1361, 1252, 1174, 1022, 963, 747 cm^{-1}; NMR ($CDCl_3$) τ 8·10 (d, J = 6, 3H), 7·76 (s, 6H), 6·59 (s, 2H), 3·60–4·23(pr of overlapping q, J = 6, 1H), 2·40–3.37 (m, 4H). (Found: C, 82·30; H, 9·57; N, 7·99. Calcd for $C_{12}H_{17}N$: C, 82·23; H, 9·87; N, 7·99.)

2-(1-*Propenyl*)N,N-*dimethylbenzylamine oxide hydrochloride* (**9**). The oxide was prepared from **14** (4·8 g; 0·0274 mol) and 85% *m*-chloroperbenzoic acid (5·52 g; 0·0274 mol) and was converted directly to the hydrochloride salt in 81% yield. The salt displayed m.p. 145–8° dec (MeOH/ether); IR (nujol) 2646, 1645, 980, 966, 889 cm^{-1}; NMR (D_2O) τ 8·03 (d, 3H), 6·50 (s, 6H), 5·08 (s, 2H), 3·49–4·13 (m, 1H), 2·33–3·33 (m, 4H). (Found: C, 63·11; H, 7·91; N, 6·03. Calcd for $C_{12}H_{18}NOCl$: C, 63·29; H, 7·97; N, 6·15).

6,7-*Dimethoxy*-1,2,3,4-*tetrahydroisoquiniline*. A soln of homoveratrylamine (30·0 g; 0·166 mol) in 50 ml water was adjusted to pH 6·0 by dropwise addition of dil HCl. To this was added 40% aqueous formaldehyde (25 ml; 0·33 mol), and the soln was warmed under N_2 on the steam bath for 1·25 hr. Conc HCl (3 ml) was added, and the mixture was warmed for an additional 0·5 hr. The red soln was cooled, basified with Na_2CO_3, extracted with 500 ml chloroform, and the extracts were washed with water, dried ($MgSO_4$) and evaporated to an orange oil. This oil crystallized from EtOH giving 20·8 g (65%) of product, m.p. 126–7° (lit[20] 84–5°). Several preparations of this material consistently melted at 126–7°.

The hydrochloride displayed m.p. 255–6° ± 2° dec depending on the rate of heating (lit[20] 253°). The picrate displayed m.p. 199–200° dec (lit[21] 203–5°).

2-*Vinyl*-4, 5-*dimethoxy*-N, N-*dimethylbenzylamine* (**15**). The methiodide was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20·8 g; 0·108 mol) and MeI (45·6 g; 0·32 mol). This salt is sparingly soluble in chloroform and was difficult to separate from NaI. It was obtained in 48% yield, m.p. 233–4° dec.

The methiodide was converted to the hydroxide by passage through a Rexyn 201(OH) resin and the resultant hydroxide pyrolyzed to give a 66% yield of **15**, b.p. 118° (0·3 mm) [lit[22] 126° (2 mm)]. After standing in the refrigerator for several days, the amine solidified to a waxy solid, m.p. 27–28·5°; picrate m.p. 158–159·5° (lit[22] 159–159·5°).

2-*Vinyl*-4, 5-*dimethoxy*-N, N-*dimethylbenzylamine oxide hydrochloride* (**10**). The *m*-chlorobenzoate salt of the oxide was prepared by treating a soln of **15** (5·13 g; 0·023 mol) in 10 ml methylene chloride at 0° with 85% *m*-chloroperbenzoic acid (4·72 g; 0·023 mol) in 20 ml methylene chloride and 30 ml anhyd ether. The mixture was warmed to 25° then evaporated at reduced pressure to a pasty solid. Addition of 50 ml anhyd ether precipitated the product, which was filtered, washed with ether and dried, yielding 8·56 g (94%), m.p. 129–30°; IR (nujol) 2750–2200, 1653, 1600, 1558, 1261, 1217, 1111, 1096, 1000–980, 914, 848, 747, 733 cm^{-1}; NMR ($CDCl_3$) τ 7·47 (broad s, 1H), 6·60 (s, 6H), 6·05 (d, 6H), 5·07 (s, 2H), 4·14–4·70 (m, 2H), 1·78–3·21 (2 complex m, 7H). (Found: C, 60·71; H, 6·16. Calcd for $C_{20}H_{24}NO_5Cl$: C, 60·99; H, 6·14.)

A soln of HCl in methylene chloride was prepared by bubbling anhyd HCl through 20–30 ml methylene chloride for 15 min. This soln was then added in 2–3 ml portions to a cold soln of the *m*-chlorobenzoate salt (2·0 g) in 20 ml methylene chloride. The HCl soln was added only until a definite pink color was imparted to pH paper. At this point, the soln was immediately evaporated at reduced pressure to a white sticky semi-solid. Anhyd ether (30 ml) was added, and the syrupy residue was stirred thoroughly for several min then filtered. This process was repeated 3 times to remove the *m*-chlorobenzoic acid. The crude chloride salt was crystallized from acetone/ether to give 1·05 g (76%) product, m.p. 135–8° dec; IR (nujol) 2450, 1587, 1256, 1209, 1093, 986, 913, 867 cm^{-1}; NMR (D_2O) τ 6·45 (s, 6H), 6·02 (s, 6H), 5·03 (s, 2H), 3·97–4·56 (m, 2H), 2·6–3·1 (m, 3H). (Found: C, 57·47; H, 7·27. Calcd for $C_{13}H_{20}NO_3Cl$: C, 57·04; H, 7·36.)

2-(1-*Chloroethyl*)-4, 5-*dimethoxy*-N, *N-dimethylbenzylamine oxide hydrochloride* (**27**). A soln of **15** (0·77 g) in 20 ml methylene chloride was cooled to 0° and anhyd HCl was bubbled through it for 10 min, producing some white solid. The soln was evaporated cold at reduced pressure to a sticky paste which was treated with ether and recrystallized from acetone to give **27** (0·49 g), m.p. 97–9° dec; IR (nujol) 3175, 2625, 1603, 1513, 1266, 1212, 1115, 1000, 982, 930, 833, 851, 753, 725; NMR (D_2O) τ 8·42 (d, 3H), 6·35 (d, 6H), 6·00 (d, 6H), 4·93 (s, 2H), 4·58 (q, 1H), 2·72 (d, 2H); NMR (DMSO) τ 8·18 (d, 3H), 6·39 (d, 6H), 6·09 (d, 6H), 4·90 (s, 2H), 3·98 (q?, 1H), 2·6 (d, 2H), 3·0 (broad s, 1H).

Reliable analysis data could not be obtained due to the instability of this compound.

This compound could also be obtained by treating **10** with excess HCl.

trans-2-*Styryl*-N,N-*dimethylbenzylamine* (**16**). A mixture of *trans*-2-stilbene carboxylic acid (23·2 g; 0·103 mol) and 20 ml redistilled thionyl chloride was warmed for 4·5 hr at 55° then overnight at 25°. After the excess thionyl

chloride was removed, 100 ml dry benzene was added, the soln was cooled to 0° and was treated with anhyd dimethylamine. A vigorous exothermic reaction occurred with precipitation of much gelatinous solid. Benzene (90 ml) was added, and the soln was saturated with dimethylamine. The flask was stoppered and the contents stirred for 3 hr at 25°. The benzene soln was extracted with sat Na_2Co_3aq then water. The aqueous phase was extracted with benzene, and the combined benzene extracts were dried ($MgSO_4$), and the benzene distilled affording 20–25 ml of an orange oil. It could not be induced to crystallize, but could be distilled with considerable loss: b.p. 171–5° (0·13 mm); IR (neat) 1629, 1590, 1104, 1066, 963, 769, 762, 690 cm^{-1}; NMR ($CDCl_3$) τ 6·86 and 7·27 (2s, 6H), 2·2–2·9 (complex m, 11H).

The crude amide (0·103 mol) in 60 ml anhyd ether was added dropwise to a stirred suspension of 7·85 g (0·205 mol) LAH in 100 ml anhyd ether at a rate to maintain reflux. After complete addition of the amide, the mixture was refluxed for 3 hr and allowed to stand at 25° overnight. The excess hydride was destroyed by addition of wet ether, then 1:1 EtOH/water. 10% NaOHaq was added, and the aqueous layer was separated, washed twice with ether and these ether extracts were combined with the ether layer. The ether extracts were then washed with water, dried ($MgSO_4$) and evaporated to 22·3 g of crude oil. The product was fractionally distilled affording 20·2 g (84% overall) of **16**: b.p. 120–3° (0·05–0·07 mm); IR (neat) 1623, 1597, 1470, 1361, 1253, 1174, 1095, 1042, 1022, 966, 841, 761, 744, 724, 691 cm^{-1}; NMR (CCl_4) τ 7·79 (s, 6H), 6·58 (s, 2H), 2·1–3·3 (complex m, 11H). On standing, the amine crystallized to a waxy solid, m.p. 26–27·5°. Picrate m.p. 158–9° (ethanol/acetone); hydrochloride (acetone/ethanol/ether) m.p. 213–213·5°.

2-*Styryl*-N,N-*dimethylbenzylamine oxide hydrochloride* (**11**). This was prepared in the same manner as **7** in 89% yield: m.p. 165–7° dec. (The m.p. was extremely dependent on the rate of heating. Consistent results were obtained by immersing the capillary into an oil bath at 100°, heating rapidly to about 15° below the m.p., then heating slowly to obtain an equilibrium value.) IR (nujol) 2558, 1626, 1587, 960, 903, 769, 749, 722, 693 cm^{-1}; NMR ($CDCl_3$) τ 6·45 (s, 6H), 4·73 (s, 2H), 2·0–2·9 (complex m, 11H).

Attempted rearrangement of 2-*vinyl* N,N-*dimethylaniline oxide hydrochloride* (**7**).

General procedure. A weighed quantity of **7** was dissolved in a measured volume of the specified reaction solvent in a flask equipped with a reflux condenser, stirrer and gas inlet tube. The system was flushed with N_2 and heated to the desired temp. At the end of the specified time the mixture was cooled, basified with NaOHaq or Na_2CO_3aq and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated *in vacuo* to viscous residues which were examined by VPC.

Unreacted starting material could be recovered by partially evaporating the aqueous phases then reacidifying with conc HCl and evaporating to dryness. The residue was boiled with several portions of EtOH and filtered from the NaCl. The filtrate was partially evaporated and the process repeated until an oily residue remained which could sometimes be recrystallized from the appropriate solvents.

A. With acetic acid/anhydrous HCl. To 6 ml of glacial AcOH saturated with dry HCl was added 0·60 g **7**. The soln was heated to 130° under N_2. After 24 hr, amine **12** was identified in the product mixture together with carbonyl impurities.

B. With acetic acid/conc HCl. To a mixture of 4 ml glacial AcOH and 2 ml conc HCl was added 0·70 g **7**, and the soln was heated to 120° under N_2 for 16 hr. Amines **12** and **17** were isolated by VPC (Column B, 115°).

Reaction of 2-*vinyl*-N,N-*dimethylaniline* (**12**) *with acetic acid*/HCl. To 50 ml AcOH saturated with dry HCl was added 4 ml freshly prepared **12**, and the mixture was heated at 125° under N_2 for 30 hr. VPC collection (Column B, 125°) of the volatile products gave recovered **12**, an unidentified 2° amine, and **18**: IR (neat) 1745, 1365, 1240, 1064–1012, 950, 755 cm^{-1}; NMR ($CDCl_3$) τ 8·50 (d, J = 7, 3H), 7·95 (s, 3H), 7·35 (s, 6H), 3·60 (q, J = 7, 1H), 2·80 (m, 4H). Minor amounts of other carbonyl compounds were present in the mixture.

Rearrangement of 2-*vinyl*-N,N-*dimethylbenzylamine oxide hydrochloride* (**8**). The procedure followed for **7** was used.

A. With acetic acid/HCl. A soln of **8** (2·0 g) in 16 ml glacial AcOH and 8 ml 12M HCl was refluxed at 125° under N_2 for 20 hr. The volatile product mixture consisted of a 4:1 mixture of **20** and **19**. Compound **20** displayed IR (neat) 1600, 1370, 1044, 1018, 926, 866, 851, 749 cm^{-1}; UV λ_{max}^{EtOH} 223 (broad), 257, 263, 270 (fine structure) mμ; NMR ($CDCl_3$) τ 8·53 (d, J = 6, 3H), 7·72 (s, 6H), 4·79 (q, J = 6, further split, 1H), 4·05 (m, 1H), 2·80 (broad s, 4H). (Found: C, 74·70; H, 8·64; N, 7·80. Calcd for $C_{11}H_{13}NO$: C, 74·54, H, 8·53, N, 7·90.)

Compound **19** displayed IR (neat) 1681, 1587, 1342, 1255, 1238, 1026, 845, 762 cm^{-1}; NMR ($CDCl_3$) τ 7·80 (s, 6H), 7·50 (s, 3H), 6·43 (s, 2H), 2·73 (unsym d, 4H). (Found: C, 74·60; H, 8·63; N, 7·82. Calcd for $C_{11}H_{13}NO$: C, 74·54; H, 8·53; N, 7·90.)

B. With 12M HCl. A soln of **8** (0·683 g) in 8 ml 12M HCl was refluxed at 123° under N_2 for 22 hr. A 1·5:1 mixture of **20** and **19** was formed.

C. With 0·12M HCl. A soln of **8** (1·30 g) in 15 ml 0·12M HCl was refluxed at 120° under N_2 for 118 hr. Only 0·128 g of ether soluble material was obtained which contained parent amine (**13**) (3%), phthalan **20** (92%) and amino ketone **19** (5%).

Reaction of 1-N,N-*dimethylamino*-3-*methylphthalan* (**20**) *with acetic acid*/HCl. To 2·5 ml of a 2:1 mixture of acetic acid/12M HCl, **20** (120 mg) was added. The mixture was heated under N_2 at 115° for 20 hr. The viscous brown oil obtained as the product showed no volatile components by VPC (Column A, 120°). Chromatography on silica gel followed by sublimation afforded a pale yellow solid, m.p. 131–4°, IR (CCl_4) 1721, 1600, 1282, 1266, 1245, 1111, 1096, 954, 864 cm^{-1}; NMR ($CDCl_3$) τ 8·38 (d, J = 6, 3H?), 5·28 (s, 1H?), 2·16–3·27 (complex m, 7H?). (Found: C, 81·74; H, 6·17. Calcd for C_9H_8O: C, 81·79; H, 6·10.) This compound has not been identified but is believed to be a dimer or higher molecular weight derivative of C_9H_8O.

Reaction of 2-*acetyl*-N,N-*dimethylbenzylamine* (**19**) *with acetic acid*/HCl. To 2·5 ml of a 2:1 AcOH/12M HCl mixture, **19** (88 mg) was added. The mixture was heated under N_2 at 115° for 20 hr. Workup afforded recovered ketone **19**.

Oxidation of 1-N,N-*dimethylamino*-3-*methylphthalan* (**20**). A soln of **20** (101 mg; 0·564 mmol) in 2 ml t-BuOH was diluted with 80 ml water, and the pH was adjusted to 7·5 with Na_2CO_3 and 10% HSO_4. A stock soln (40 ml) of $NaIO_4$/$KMnO_4$ (20·8 g $NaIO_4$ and 0·395 g $KMnO_4$ per liter) was added, and the soln was stirred at 25° for 21 hr. It was

then filtered, and the filtrate was extracted with ether. The aqueous layer was acidified with 10% H_2SO_4 and extracted with ether to give 88 mg of a semisolid. Trituration with pentane precipitated 30 mg of a tan solid, m.p. 108–111°, recrystallized twice from benzene/pentane to m.p. 112–3°; mixed m.p. with authenic 2-acetylbenzoic acid 113–5°. Its IR was identical to authenic material also.

Reduction of 1-N,N-*dimethylamino*-3-*methylphthalan* (**20**)

A. With sodium borohydride. Water (2 ml) $PtCl_4$ soln (0·2 ml; 1 g $PtCl_4$ in 20 ml water), Norit (0·1 g) and a magnetic stirrer were placed in a small filter flask with a rubber bulb wired to the side arm. To this was added stabilized $NaBH_4$ soln (0·6 ml, prepared from 0·8 g $NaBH_4$ and 0·15 g NaOH in 20 ml water). The soln was allowed to stand 5 min to generate the catalyst then 0·8 ml conc HCl and a soln of **20** (185 mg) in 2 ml 50% aqueous EtOH was added, and a serum cap was wired onto the mouth of the flask. The soln was stirred at 30° while 0·3 ml of the borohydride soln was added via a syringe through the stopper. After 40 min another 0·3 ml was added, and the mixture was stirred an additional 11 hr.

The catalyst was removed by filtration and washed with water. The filtrate was basified with 30% NaOH and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$), and evaporated to a yellow liquid. Compound **23** was isolated by VPC collection (Column A, 120°): IR (neat) 3380, 3150, 1090, 1044, 1010, 898, 838, 744, 729 cm^{-1}; UV λ_{max}^{EtOH} 222, 261, 266 (sh), 270 (infl) mμ; NMR ($CDCl_3$) τ 8·42 (d, J = 7, 3H), 7·80 (s, 6H), 6·47 (AX quartet, J = 12, 2H), 5·05 (q, J = 7, 1H), 2·6–3·0 (m, 4H). (Found: C, 73·70; H, 9·53; N, 8·12. Calcd for $C_{11}H_{17}NO$: C, 73·70; H, 9·56, N, 7·81).

A small amount of a second component was isolated which displayed IR (neat) 1357, 1250, 1170, 1042, 1021, 863, 754 cm^{-1} suggesting 2-ethyl-N,N-dimethylbenzylamine, a product of further hydrogenation.

B. Catalytic hydrogenation. Platinum on carbon (Englehard) (10–20 mg) in 5 ml 95% EtOH was placed in a small flask and attached to the hydrogenation apparatus. The system was flushed with H_2 then **20** (125·8 mg; 0·711 mmol) in 10 ml of 95% EtOH containing 3 drops AcOH was added dropwise. After 4 hr the catalyst was filtered, and the mixture was poured into water, basified with 3 drops of 30% NaOH and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and concentrated to an oil which contained two volatile components: unreacted **20** and alcohol **23**.

Reduction of 2-*acetyl*-N,N-*dimethylbenzylamine* (**19**). To a soln of **19** (62 mg; 0·356 mmol) in 2 ml dry MeOH was added a soln of $NaBH_4$ (25 mg; 0·7 mmol) in 2 ml dry MeOH. The mixture was stirred at 25° for 1·25 hr then diluted to 30 ml with water and acidified with 6M HCl to destroy the excess borohydride. The mixture was rebasified with 20% NaOH, extracted with ether, dried ($MgSO_4$) and concentrated to 27 mg crude **23**, which was purified by VPC (column A, 110°).

Acid-catalyzed hydration of 2-*vinyl*-N,N-*dimethylbenzylamine* (**13**). Amine **13** (1 ml) was dissolved in 25 ml 25% H_2SO_4aq and refluxed under N_2 for 6 days. The mixture was cooled, basified with Na_2CO_3 and extracted with ether. The dried ether soln was concentrated to 0·8 g of yellow oil. VPC purification (column B, 190°) yielded about equal quantities of unreacted **13** and alcohol **23**. Recovery from VPC was poor indicating the presence of higher molecular weight substances.

Reaction of 2-*vinyl*-N,N-*dimethylbenzylamine* (**13**) *with acetic acid*/HCl. To a mixture of 10 ml glacial AcOH and 5 ml conc HCl, **13** (0·6 g) was added, and the soln was refluxed under N_2 for 24 hr. The clear yellow soln was worked up as usual to give 0·5 g pale yellow oil. VPC collection (column D, 115°) of the three major components gave unreacted **13** (76 mg) 2-(1-acetoxyethyl)N,N-dimethylbenzylamine (13 mg): IR (neat) 1727, 1360, 1238, 1064–1017, 763 cm^{-1}; NMR ($CDCl_3$) τ 8·55 (d, J = 7, 3H), 8·03 (s, 3H), 7·81 (s, 6H), 6·5 (AX q, J = 12, 2H), 3·82 (q, J = 7, 1H), 2·5–3·0 (m, 4H); and 44 mg alcohol **23**.

Rearrangement of 2-(1-*propenyl*)-N,N-*dimethylbenzylamine oxide hydrochloride* (**9**)

A. With 12M HCl. **9** (1 g) was dissolved in 20 ml conc HCl, and the soln was refluxed under N_2 at 119° for 39 hr. Work-up afforded 0·54 g yellow liquid which VPC (column A, 130°) showed to contain two major and two minor components. The major products were collected (column C, 130–5°) and shown to be **24** (0·075 g) and **25** (0·21 g).

Compound **24** displayed IR (neat) 1686, 1590, 1359, 1340, 1214, 1026, 957, 847, 759 cm^{-1}; NMR ($CDCl_3$) τ 8·83 (t, J = 7, 3H), 7·82 (s, 6H), 7·20 (q, J = 7, 2H), 6·45 (s, 2H), 2·63 (s, 4H). (Found: C, 75·53; H, 9·18; N, 7·40. Calcd for $C_{12}H_{17}NO$: C, 75·35; H, 8·96; N, 7·32.)

Compound **25** displayed IR (neat) 1377, 1041, 963, 900, 751 cm^{-1}; NMR ($CDCl_3$) τ 8·80–9·26 (q or 2 overlapping t, 3H), 7·98–8·50 (m, 2H), 7·67 (d, 6H), 4·63–5·13 (m, 1H), 3·98 (m, 1H), 2·70 (broad s, 4H). (Found: C, 75·45; H, 9·30; N, 7·45. Calcd for $C_{12}H_{17}NO$: C, 75·35; H, 8·96; N, 7·32.)

B. With acetic acid/HCl. A soln of **9** (1·06 g) in 12 ml glacial AcOH and 6 ml 12M HCl was refluxed at 117° under N_2 for 45 hr. Workup afforded 0·176 g brown liquid which gave **25** (32 mg) and **24** (18 mg), and an unidentified oil (5 mg) on VPC collection (Column C, 136°).

C. With 6M HCl. A soln of **2** (0·40 g) in 10 ml 6M HCl was refluxed under N_2 at 112° for 22 hr. Workup gave a yellow liquid (0·128 g) which was mainly **25**.

Rearrangement of 2-*vinyl*-4,5-*dimethoxy*-N,N-*dimethylbenzylamine oxide hydrochloride* (**10**) *and its addition product* (**27**)

Because of the instability of both hydrochlorides, they were prepared fresh from the *m*-chlorobenzoate salt for each run.

A. Rearrangement of **10** *with* 12M HCl. A soln of **10** (1·04 g) in 20 ml 12M HCl was heated at 85° under N_2 for 50 min. Workup gave a viscous yellow oil (0·595 g). This material was unstable on the VPC and on silica gel columns and thin layer plates. It was purified by alumina chromatography. Elution with 1:1 pentane/ether afforded a thick colorless oil identified as **28**: IR (neat) 3500, 1383, 1326, 1276, 1222, 1125, 1093–1015, 983, 930, 887–833, 787 cm^{-1}; NMR ($CDCl_3$) τ 8·53 (d, 3H), 7·67 (s, 6H), 6·08 (s, 6H), 4·75 (m, 1H), 4·03 (m, 1H), 3·13–3·30 (m, 2H). (Found: C, 65·31; H, 7·78. Calcd for $C_{13}H_{19}NO_3$: C, 65·80; H, 8·07.)

Later fractions eluted with chloroform gave a small amount of a thick yellow oil which contained several materials, none of which were identified.

The *m*-chlorobenzoate salt of the oxide behaved similarly in 12M HCl.

B. Rearrangement of **27**. **27** (1 g) was dissolved in 20 ml 12M HCl and heated under N_2 at 97° for 1·5 hr. Workup afforded a viscous oil (0·513 g) identified as **28**.

When **27** was treated with 5% NaOHaq at 71°, an oil separated within 2 min which was also identified as **28**.

Rearrangement of 2-styryl-N,N-dimethylbenzylamine oxide hydrochloride (**11**)

12M HCl (50 ml) and **11** (2·09 g) were refluxed under N_2 at 134° for 48 hr. Workup afforded 524 mg red oil showing 4 components on VPC (column E, 190°). These materials were collected with incomplete resolution owing to their long retention times and excessively broad peaks. Analytically pure samples of the major components were not obtained, but identification was possible through comparison with authentic materials.

Peak number one, 10% of the mixture, was tentatively identified as **32** and/or **33**: IR (neat) 1770, 1680 (weak, probably carbonyl impurity), 1600, 1450, 1380, 1036, 1002, 930–900, 853, 758, 701 cm^{-1}; NMR ($CDCl_3$) τ 7·65 (d, 6H), 6·80–6·98 (d of t?, 2H), 4·4–4·8 (m, 1H), 3·9–4·1 (m, 1H, 2·55–2·78 (m, 9H).

Peak two, 12% of the mixture, could not be obtained completely free of peak three, but is identified as **31**[11]: IR (neat) 1757 (weak carbonyl impurity), 1695–1656, 1595, 1258, 1205, 1176, 1032, 994, 885, 867, 849, 763, 694 cm^{-1}; NMR ($CDCl_3$) τ 7·70, 7·85, (2s, 6H), 6·41 (s, 2H), 5·85 (s, 2H), 2·2–2·8 (complex m, 9H).

Peak three, 78% of the mixture, was identified as **30**: IR (neat) 1689, 1590, 1575, 1443, 1326, 1255, 1211, 1172, 1095, 1022, 994, 846, 756, 743, 690 cm^{-1} (lit[10] 1690, 845, 753, 740, 690 cm^{-1}); NMR ($CDCl_3$) τ 8·03 (s, 6H), 6·65 (s, 2H), 5·58 (s, 2H), 2·4–2·8 (m, 7H), 1·8–2·05 (m, 2H). This material was synthesized[10] for direct comparison.

A very small amount of a fourth component (peak four) was present. This material appeared to be decomposing during collection.

The aqueous phase, after removal of the ether-soluble material, was acidified with HCl and treated with brine to salt out the organic material. It was then extracted with chloroform to give a salt extract which contained varying mixtures of recovered **11** and a hygroscopic quaternary salt which has not yet been identified: IR (KBr) 3390, 1613 (water), 1450, 1258, 990, 957, 926, 881, 847, 803, 770, 730, 704 cm^{-1}.

The product ratios in this reaction varied with time as shown in the Table below (for a 7 g sample of **11**).

Reaction time (hr)	Ether soluble material (g)	% Peak 1 (32 or 33)	% Peak 2 (31)	% Peak 3 (30)	% Peak 4	$CHCl_3$ Extract (g)	Total (g)
15·5	0·143	30·7	1·8	56·5	11·0	0·72	0·86
24·5	0·453	18·5	10·0	70·5	< 1	1·10	1·55
43·5	0·536	2·4	22·3	74·8	< 1	1·85	2·39
64·0	0·352	< 1	25·9	72·7	< 1	0·95	1·29
							6·09

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