Tertiary Amine Oxide Rearrangements. II. N-Benzyldimethylamine Oxides as Models for the Demethylation of Nicotine[1]

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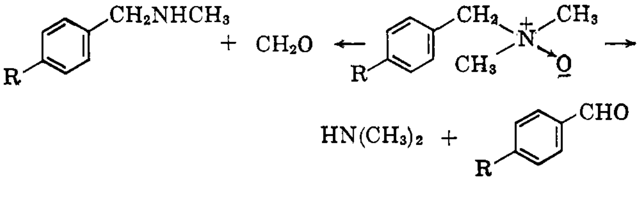
The metal-complex catalyzed rearrangement of N-benzyldimethylamine oxide and of N,N-dimethyl-*p*-nitrobenzylamine oxide has been shown to proceed concurrently along two pathways to yield formaldehyde and the appropriate benzaldehyde, in a ratio determined by the statistical ratio of the number of available α-protons (*i.e.*, adjacent to nitrogen) and by their relative acidities.

It was proposed earlier[3] that the metal complex catalyzed rearrangement of trimethylamine N-oxide occurs in two 1-electron steps involving the formation of an intermediate amminium ion radical. *t*-Amine oxides occur widely in both animals and plants,[4] and the biosynthesis of trimethylamine N-oxide from trimethylamine has been demonstrated recently.[5] The bacterial and biochemical degradation of nicotine gives "oxynicotine" (nicotine N-oxide) as the first product[6] and, before applying the mechanism of the *t*-amine oxide rearrangement[3] to explain the metabolism of nicotine, it was necessary to investigate the rearrangement of unsymmetrical *t*-amine oxides. N-Benzyldimethylamine oxide[7] and N-*p*-nitrobenzyldimethylamine oxide were chosen as models for the demethylation of nicotine. The iron(III)–tartaric acid system was used, since previous work[3] showed that substantial rearrangement took place in the pH range 5 to 9, and the reaction was studied at pH 6.3. In each case, two competing reactions may occur, leading to formaldehyde and the appropriate benzaldehyde in a ratio determined by (1) the statistical ratio of the number of available α-protons, (2) the increased acidity of the benzylic hydrogens, (3) the steric hindrance offered by the benzene ring to an approach to the benzylic hydrogen atoms, and (4) the effect of molecular size on the stability of the intermediate amminium ion radical.

The reactions investigated in this work are shown.



Experimental[8]

N-Benzyldimethylamine oxide[7] was a hygroscopic solid, stored as the picrate, m.p. 159–160.5° (lit.[7] m.p. 159.4–160°).

N,N-Dimethyl-*p*-nitrobenzylamine.—A mixture of 21 g. (0.1 mole) of *p*-nitrobenzyl bromide in 100 ml. of benzene and 0.5 mole of dimethylamine was allowed to reflux for 2 hr. on the steam bath, and the resulting dimethylamine hydrobromide was filtered off (9.2 g., 74%). Evaporation of the filtrate left 12.3 g. (67%) of the base as an oil. The picrate had m.p. 148–149° (lit.[9] m.p. 149°).

N,N-Dimethyl-*p*-nitrobenzylamine Oxide.—A mixture of 12.3 g. of N,N-dimethyl-*p*-nitrobenzylamine and 20 ml. of 30% hydrogen peroxide was stirred at room temperature for 24 hr., and the resulting homogeneous mixture was concentrated under vacuum, in the presence of platinum gauze to destroy residual peroxide. The residue was converted into the picrate, which was crystallized from aqueous ethanol, m.p. 178–180°.

Anal. Calcd. for $C_{15}H_{15}N_5O_{10}$: C, 42.56; H, 3.10; N, 16.55. Found: C, 42.81; H, 3.38; N, 16.49.

N-Methyl-*p*-nitrobenzylamine.—A solution of 7 g. (0.033 mole) of *p*-nitrobenzyl bromide in 100 ml. of ethanol saturated with methylamine was heated under reflux for 5 hr. while methylamine gas was passed through the reaction mixture. After removal of ethanol the residue was partitioned between dilute hydrochloric acid and ether. The aqueous layer was made basic and extracted with ether, and the residue on removal of the ether was converted into the picrate; the yield was 4.4 g. (33%), m.p. 146–147.5°, from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_5O_9$: C, 42.54; H, 3.32; N, 17.72. Found: C, 42.83; H, 3.38; N, 17.60.

A mixture melting point with N,N-dimethyl-*p*-nitrobenzylamine picrate (m.p. 148–149°) showed a marked depression (126–140°). N-Methyl-*p*-nitrobenzylamine hydrochloride had m.p. 228–233° (lit.[10] m.p. 219°).

Conversion of the N-Oxide Picrates to the Free Bases on Alumina.—The amine oxides could not be prepared free from water. A known weight of the picrate was therefore converted to the free base, and this was used directly in the ferric ion induced rearrangement.

A. **N,N-Dimethylbenzylamine Oxide.**—The picrate (0.002 mole) was dissolved in 350 ml. of chloroform and passed through a column containing 30 g. of Merck's alkaline alumina, and the alumina was washed with 500 ml. of 30% methanol in chloroform. When the last fractions of the eluate failed to give a positive reaction with picric acid, the solvents were evaporated under reduced pressure below 50°. Conversion of the eluted base to the picrate in one instance gave back the original picrate in 99% recovery.

B. **N,N-Dimethyl-*p*-nitrobenzylamine Oxide.**—The picrate (0.001 mole) was placed on the top of 30 g. of Merck's alkaline alumina in a chromatographic column. The free base was eluted with 1200 ml. of 30% methanol in chloroform in the manner described above.

Rearrangement of the N-Oxide with Ferric Ion and Tartaric Acid.—The amine oxide obtained from the picrate was dissolved in about 15 ml. of distilled water. The N,N-dimethylbenzylamine N-oxide was added to actual volume of a solution of 0.006 mole of iron(III) nitrate 9-hydrate and 0.06 mole of L(+)-tartaric acid. The N,N-dimethyl-*p*-nitrobenzylamine oxide was added to a similar volume of a solution of 0.003 mole of iron(III) nitrate 9-hydrate and 0.03 mole of L(+)-tartaric acid. The pH of the solutions was adjusted to 6.3 with a saturated solution of sodium carbonate, the final volume not exceeding 50–60 ml. The solutions were kept at 80° for 40 min. and then cooled in ice.

Identification and Determination of the Products of the Rearrangement.[11] **A. N,N-Dimethylbenzylamine Oxide. I. Formaldehyde and Benzaldehyde by 2,4-Dinitrophenylhydrazine.**

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[8] All reagents were of analytical reagent grade. Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Microanalyses were by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley 4, Calif. Ultraviolet spectra were determined on a Beckman DU spectrophotometer.

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[11] The determinations described in sections A I, II, III and IV were performed on separate runs, as were those described in sections B I and II.

(i) **Total Aldehydes.**—The 2,4-dinitrophenylhydrazine reagent[3] (100 ml.) was added to the reaction solution (pH 6.3), chilled at 5°, and shaken vigorously for 3 min. The precipitate was filtered, washed (distilled water), and dried overnight at 70–80°. In blank experiments it was found that this procedure gave a 98% recovery of both formaldehyde and benzaldehyde 2,4-dinitrophenylhydrazones.

(ii) **Preparation of Standard Curves for Ultraviolet Estimation.**—The absorption maximum of formaldehyde 2,4-dinitrophenylhydrazone was at 345 and that of benzaldehyde 2,4-dinitrophenylhydrazone at 377 mμ.[12] The absorbancies of chloroform solutions of the pure 2,4-dinitrophenylhydrazones, in concentrations ranging from 0.01–0.07 mg./10 ml., were determined at the absorption maximum. A standard curve for each compound gave a straight line over the concentration range used.

(iii) **Separation of 2,4-Dinitrophenylhydrazone Mixture by Thin Layer Chromatography.**—Thin layer chromatography, using a 250-μ layer of silica gel G, was carried out with 0.03-ml. portions of a solution containing 25 mg. of the 2,4-dinitrophenylhydrazone mixture in 10 ml. of chloroform. The chromatogram was developed in a mixture of benzene and hexane (3:1 by volume). The mixture separated into two spots whose R_f values were identical with those of pure samples of formaldehyde (R_f 0.28) and benzaldehyde (R_f 0.47) 2,4-dinitrophenylhydrazones.

(iv) **Determination of Individual 2,4-Dinitrophenylhydrazones.**—The silica gel containing each of the separated spots was scraped off with a razor blade into a beaker, stirred with chloroform, filtered, and washed with chloroform to give 10 ml. of filtrate in a volumetric flask. From its absorbance, the amount of each 2,4-dinitrophenylhydrazone was determined from the corresponding standard curve. The recovery from the silica gel of known concentrations of pure 2,4-dinitrophenylhydrazones was 99.9%, and the ratios obtained were calculated on the basis of complete recovery of the 2,4-dinitrophenylhydrazones from the silica layer.

II. **Formic Acid.**—After the reaction solution (pH 6.3) was chilled to 5°, it was acidified by the addition of 5 ml. of 5 *N* hydrochloric acid and then 0.75 g. of magnesium shavings[3] was added. After a reduction period of 25 min. at 5°, the solution was filtered rapidly from any excess magnesium, and 161 ml. of 0.4% aqueous dimedone reagent was added. The solution was shaken vigorously for 10 min., set aside for 24 hr., and filtered; the precipitate was washed with distilled water and dried to a constant weight at 60–70°. The reduction with hydrochloric acid and magnesium did not increase the amounts of dimedone precipitate, indicating the absence of formic acid in the reaction solution. Formic acid alone under the same conditions was almost completely reduced to formaldehyde.

III. **Benzoic Acid.**—The pH of the reaction solution chilled to 5° was adjusted to 2 with 50% sulfuric acid. The solution was then extracted with two 50-ml. portions of benzene and the benzene layer was washed with four 25-ml. portions of potassium bicarbonate solution. The water layer was separated, brought to pH 0 with 50% sulfuric acid, and extracted again with four 50-ml. portions of benzene. The benzene extract was finally evaporated under reduced pressure. No residue of benzoic acid was noticed. In a blank experiment on 0.001 mole of benzoic acid, this procedure gave 99–100% recovery.

IV. **N-Methylbenzylamine and N,N-Dimethylbenzylamine.**—The reaction solution, after cooling, was brought to pH 12 with a concentrated solution of sodium hydroxide, and continuously extracted with benzene for 48 hr. The benzene was evaporated under reduced pressure and a 1% solution of the extract in benzene was prepared.

Thin layer chromatography on a plate coated with silica gel G was carried out with 0.03 ml. each of the 1% benzene extract, the N-methylbenzylamine, and the N,N-dimethylbenzylamine. The plate was developed in a mixture of *n*-butyl alcohol–glacial acetic acid–water (60:15:25) and the amines were identified with 0.1% potassium permanganate solution which gave yellow spots on a violet background,[13] and with Dragendorff's reagent which colored the spots dark orange. The extract showed only one spot, identical with N-methylbenzylamine. N,N-Dimethylbenzylamine was not detected in the extract. The R_f values of the secondary and tertiary amines in the solvent system used were 0.55 and 0.44, respectively.

The benzene extract was also examined by gas–liquid chromatography, using a column 2 m. long and internal diameter of 5 mm. packed with 25% polyethylene glycol (mol. wt. 20,000) on Chromosorb W. The support was previously washed with 2% alcoholic potassium hydroxide, followed by methanol, and dried at 100°; 1 μl. of a 1% solution in benzene each of the N-methylbenzylamine and the N,N-dimethylbenzylamine was injected. The N-methylbenzylamine was not eluted from the column, owing probably to hydrogen bonding of the amine with polyethylene glycol.[14] The N,N-dimethylbenzylamine had a retention time of 2.2 min. at 127° and 9.9 min. at 82°. Under the same conditions, 1 μl. of the 1% benzene extract showed no peak for either N-methylbenzylamine or N,N-dimethylbenzylamine (the secondary amine, shown to be present in the benzene extract by thin layer chromatography, stays on the polyethylene glycol). No tertiary amine was therefore present.

B. **N,N-Dimethyl-*p*-nitrobenzylamine Oxide. I. Formaldehyde and *p*-Nitrobenzaldehyde by 2,4-Dinitrophenylhydrazine.**—To the N,N-dimethyl-*p*-nitrobenzylamine N-oxide reaction solution (pH 6.3), chilled to 5°, 50 ml. of the 2,4-dinitrophenylhydrazine reagent was added and the solution was treated as described above. The 2,4-dinitrophenylhydrazones of formaldehyde and *p*-nitrobenzaldehyde were identified and determined by thin layer chromatography and spectrophotometry. A silica gel G layer 750 μ thick was used since the 250-μ coating produced tailing of the *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone. In the solvent system used (benzene–hexane, 3:1), the R_f value of formaldehyde 2,4-dinitrophenylhydrazone was 0.23 and that of *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone was 0.14. The 2,4-dinitrophenylhydrazones were eluted with chloroform and determined against a chloroform blank at 345 mμ for formaldehyde 2,4-dinitrophenylhydrazone and 382 mμ for *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone.[15] The amount of each present was then calculated, using a standard curve prepared as before.

II. **N-Methyl-*p*-nitrobenzylamine and N,N-Dimethyl-*p*-nitrobenzylamine.**—The reaction solution (pH 6.3) was made alkaline and continuously extracted as before. A 1% solution in benzene of the residue was prepared and examined by thin layer chromatography for the presence of N-methyl-*p*-nitrobenzylamine and N,N-dimethyl-*p*-nitrobenzylamine, as described above. The spots were identified with Dragendorff's reagent. Only one spot, whose R_f value was identical with that of pure N-methyl-*p*-nitrobenzylamine, was found. The R_f values of the secondary and tertiary amines in the solvent system used were 0.55 and 0.49, respectively.

Results and Discussion

Results are given in Table I.

TABLE I

RESULTS OF TERTIARY AMINE OXIDE REARRANGEMENTS[a]

	N,N-Dimethylbenzylamine oxide	N,N-Dimethyl-*p*-nitrobenzylamine oxide
Total mixed 2,4-DNP,[b] mg.	242.5	100.4
Ratio by wt. of formaldehyde to aromatic aldehyde 2,4-DNP	1.7:1	1:2.8
Amount of formaldehyde 2,4-DNP, mg. (mmoles)	152.7 (0.72)	26.4 (0.13)
Amount of aromatic aldehyde 2,4-DNP, mg. (mmoles)	89.8 (0.31)	74.0 (0.22)
Yield of total aldehydes, %	51.5	35
Ratio by molecules of formaldehyde to aromatic aldehyde	2.3:1	0.57:1

[a] All results are the average for five determinations, each duplicated, and reproducible to within 5%. [b] DNP = dinitrophenylhydrazone.

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In the rearrangement of N,N-dimethylbenzylamine oxide, if the rates of both reactions were equal, the ratio of formaldehyde to benzaldehyde would be 3:1, from the statistical ratio of the number of available protons. The observed ratio of 2.3:1 thus indicates an effect due to the increased acidity of the benzylic hydrogen, and despite any steric hindrance of that hydrogen caused by the presence of the aromatic ring. The rearrangement of N,N-dimethyl-*p*-nitrobenzylamine oxide gave the much lower observed molecular ratio of 0.57:1 of formaldehyde to *p*-nitrobenzaldehyde. Since the steric situation is unchanged in the two cases, and the number of available protons is identical, this difference in the observed ratio must reflect the markedly greater acidity of the benzylic proton in the latter case.

The absence of either formic acid or of the appropriate benzoic acid from the products of the reaction indicated that a reduction of some N-oxide by formaldehyde or by the benzaldehyde did not occur during this rearrangement. This conclusion was further supported by the detection by thin layer chromatography of the presence of N-methylbenzylamine and of N-methyl-*p*-nitrobenzylamine, respectively, and by the absence of N,N-dimethylbenzylamine and N,N-dimethyl-*p*-nitrobenzylamine.

The above results show that the rearrangement of an unsymmetrical tertiary amine oxide may occur concurrently along several pathways, and that (in the absence of marked steric hindrance) the ratio of the possible reaction rates will be determined, *inter alia*, by the relative acidities of the available protons. In cases in which one type of proton is significantly sterically hindered, this may also be expected to influence the relative rates of rearrangement. The application of these results to the demethylation of nicotine, in which such a situation obtains, was described in a preceding communication.[16]

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Potential Carcinolytic Agents. II. Fluoroethylamines by Reduction of Fluoroacetamides with Diborane[1]

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The reduction af aliphatic amides by diborane gives amines in good yields. This method is especially suitable for reducing fluoroacetamide and N-substituted fluoroacetamide derivatives where lithium aluminum hydride and lithium aluminum hydride–aluminum chloride cause hydrogenolysis of the C–F bond.

In our studies of new deactivated alkylating agents,[2] bis(2-fluoroethyl)amine (IIc) and 2-chloro-2′-fluorodiethylamine (IIb) were required as starting materials, but the reported[3] synthetic methods involving the reaction of 2-chlorofluoroethane, 2-bromofluoroethane, or 2-fluoroethyl benzenesulfonate with ammonia or amines appeared to be cumbersome and are known to yield mixtures of amines in rather low yields.

The preparation of IId by reduction of Id with lithium aluminum hydride has been claimed by Olah and Pavlath.[4] We attempted to extend this reaction and to prepare the desired amines II by the reduction of the corresponding amides I.

$$\underset{\text{I}}{FCH_2CONHR} \longrightarrow \underset{\text{II}}{FCH_2CH_2NHR}$$

a, R = CH_2CH_2OH
b, R = CH_2CH_2Cl
c, R = CH_2CH_2F
d, R = H

Treatment of Ia with lithium aluminum hydride in refluxing tetrahydrofuran for 1 hr. yielded mostly unreacted amide. When the reaction mixture was refluxed for 5 hr., N-ethyl-2-aminoethanol was obtained in 60% yield. Reduction of Id with lithium aluminum hydride in ether solution, in an attempt to duplicate the exact conditions described by Olah and Pavlath,[4] yielded ethylamine as the only identifiable product.

The easy hydrogenolysis of the C–F bond in these reactions is in accordance with the observation of Pattison, *et al.*,[5] who mentioned that particularly low yields of the desired fluoroalkylamines were obtained in the attempted lithium aluminum hydride reduction of ω-fluoronitriles having less than five carbon atoms.

Hydrogenolysis of the C–F bond was also obtained in the reduction of Ib with lithium aluminum hydride–aluminum chloride reagent[6] and 2-chlorodiethylamine was obtained in 33% yield. Very recently Pettit and Smith[7] confirmed our observation that this reagent causes hydrogenolysis of the C–F bond. These authors reported that reduction of the amide group without hydrogenolysis of the C–F bond was effected when N-bis(2-fluoroethyl)-3,4,5-trimethoxybenzamide was treated with lithium aluminum hydride for 24 hr. at room temperature. We found that this method was unsuccessful for reducing fluoroacetamide (Id); all the starting material was recovered unchanged.

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