pound If was identified by characterization of the 2,4-dinitrophenylhydrazone; Id was identified by infrared and n.m.r. spectra taken on the crude compound and characterization of the pure 2,4-dinitrophenylhydrazone.

Preparation of Dialkyl Aroylphosphonate 2,4-Dinitrophenylhydrazones.—The data in Table II were accumulated in experiments performed in essentially the following manner. A stock solution of 2,4-dinitrophenylhydrazine was prepared by placing 6 g. of the reagent (m.p. 198–199°) in 30 ml. of concentrated sulfuric acid and adding this mixture to 40 ml. of water and 140 ml. of 95% ethanol. To 25 ml. of this solution was added 0.5 g. of the dialkyl aroylphosphonate to give a precipitate of the corresponding highly colored 2,4-dinitrophenylhydrazone. Methanol was used to recrystallize all of the derivatives.

Acid Hydrolysis of Dimethyl *p*-Anisoylphosphonate (Ib).—A flask was charged with 2.44 g. (0.01 mole) of Ib and 10 ml. of 0.1 *N* hydrochloric acid. The reaction mixture was stirred for 4 hr. at room temperature without any noticeable change in composition. After stirring for 24 hr. the mixture deposited 1.50 g. (98.7%) of *p*-anisic acid.

Basic Hydrolysis of Dimethyl *p*-Anisoylphosphonate (Ib).—In a system identical with that used for acid hydrolysis was added 2.44 g. (0.01 mole) of Ib and 10 ml. of 0.1 *N* sodium hydroxide. Within 15 min. a heavy white precipitate was observed in the reaction mixture. The solid material was filtered off and the free *p*-anisic acid was regenerated from its sodium salt by treatment with 0.1 *N* hydrochloric acid. The acid (1.43 g., 94.1%) had m.p. 184° after recrystallization from ether.

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Tertiary Amine Oxide Rearrangements. III. The Mechanism of the Demethylation of Nicotine[1]

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The metal complex catalyzed rearrangement of nicotine N-oxide has been shown, by the combined use of thin layer and gas chromatography, to yield formaldehyde and nicotine, N-methylmyosmine, nornicotine, myosmine, nicotyrine, and cotinine. A simple unified mechanism is capable of rationalizing the formation of these nicotine alkaloids, as well as of all other known metabolites of nicotine.

Nicotine (I) is metabolized in animals and plants to give a variety of products of which only nornicotine (II) may be accounted for by a simple demethylation. Other metabolic products of nicotine include: nicotine 1'-oxide (III) ("oxynicotine"),[3] 3-methylaminopropyl 3'-pyridyl ketone (IV) ("pseudooxynicotine"),[4] 3-nicotinoylpropionic acid (V),[4,5] N-methylmyosmine (VI)[6] (which in aqueous solution is present, by a reversible dehydration–hydration, in equilibrium with IV in the form of its cyclic aminoketal IVa), nicotyrine (VII),[3d,6c,7] γ-3-pyridyl-γ-methylaminobutyric acid (VIII)[8–10] (which cyclizes spontaneously at pH 7 into its lactam cotinine (IX)[11,12]), desmethylcotinine (X),[9,11] γ-3-pyridyl-γ-oxo-N-methylbutyramide (XI),[13] γ-3-pyridyl-γ-hydroxybutyric acid (XII),[14] and myosmine (XIII), a naturally occurring nicotine alkaloid[15] also formed by autoxidation of nicotine.[3d]

In the preceding paper[16] the rearrangement of N-benzyldimethylamine oxides was shown to proceed concurrently along two pathways giving formaldehyde and the appropriate benzaldehyde, in a ratio determined (in the absence of steric factors) by the available α-protons (*i.e.*, adjacent to nitrogen) and by their relative acidities. In the case of nicotine 1' oxide (III), this rearrangement may occur in the following three possible ways, since three different types of α-proton exist in III: A. Loss of the proton from the N-methyl group, leading to the methylolamine (XIV) known to give formaldehyde and nornicotine (II). Since there are three such protons available, this reaction will have a high statistical probability and is the expected route for N-demethylation. Nicotine-methyl-^{14}C has been found to give radioactive respiratory carbon dioxide *in vivo*,[17] in agreement with the expected conversion of formaldehyde to carbon dioxide *via* formic acid.

B. Another pathway, on the basis of the rearrangement of the N-benzyldimethylamine oxides,[16] is by loss of a proton from the α-position adjacent to the pyridine ring, giving a tertiary hydroxynicotine (IVa), the cyclic ketal of 3-methylaminopropyl 3'-pyridyl ketone (IV). The expected facile dehydration of the tertiary hydroxyl would give the conjugated N-methylmyosmine (VI).

C. Proton removal from the other α-position of the pyrrolidine ring gives a new secondary hydroxynicotine (XV), the cyclic acetal of α-3-pyridyl-γ-methylaminobutyraldehyde (XVa). Ready dehydrogenation of this aldehyde to the acid yields the known γ-3-pyridyl-γ-methylaminobutyric acid (VIII), easily ring closing to form its lactam, cotinine (IX), which may also arise directly from an oxidation or dehydrogenation of the cyclic acetal XV. Nicotine metabolism in rabbit[18] forms a hydroxynicotine with the properties of a cyclized

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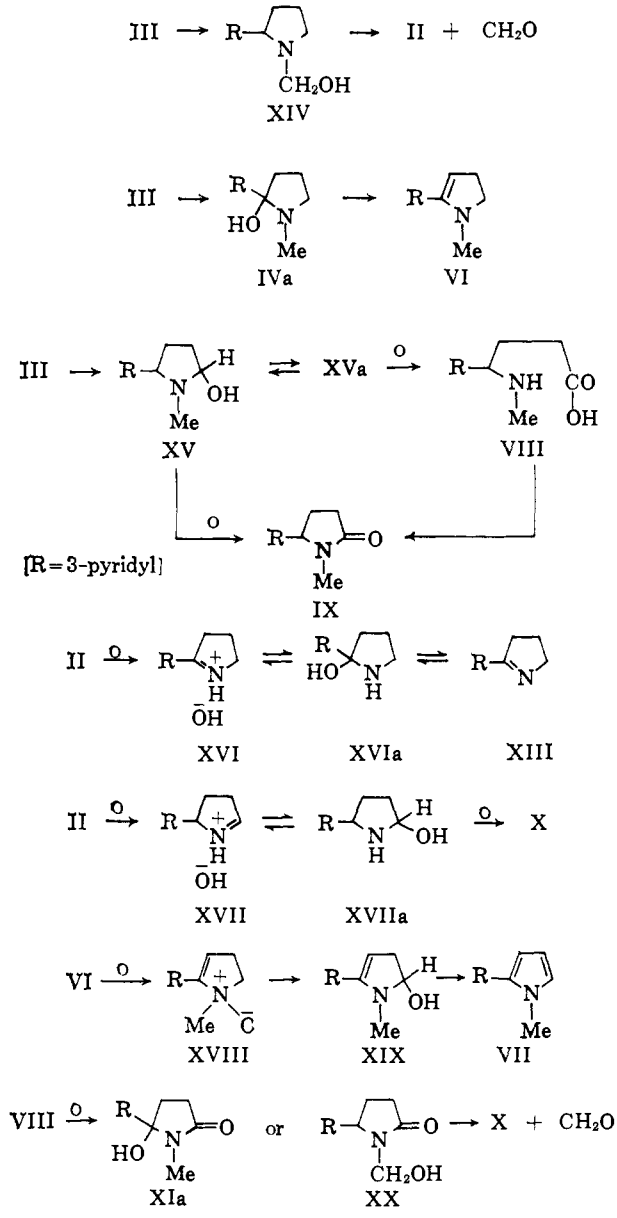
aminoaldehyde, which must be the system XV ⇌ XVa and undergoes oxidation to cotinine (IX). Moreover, the dehydrogenation XV → IX is not without precedent[19] and is inhibited by cyanide, suggesting[18] an aldehyde oxidase catalyst.

These three simple cases explain the formation of the bulk of the known metabolites of nicotine. An extension of the same mechanism can account for the others. The dehydrogenation of pyrrolidines into 1-pyrrolines is known both chemically[20] and biologically,[21] and thus nornicotine (II) can form myosmine (XIII) (which readily yields carbonyl derivatives[22]) *via* the plausible intermediates XVI and XVIa. Dehydrogenation of nornicotine (II) in the other direction would afford, *via* XVII, the cyclic aminoketal XVIIa, in equilibrium with γ-amino-γ-3-pyridylbutyraldehyde (XVIIb), readily oxidized to the known[23] lactam desmethylcotinine (X). Repetition of the oxidation sequence by N-methylmyosmine (VI) followed by rearrangement of the N-oxide XVIII to XIX would on dehydration afford nicotyrine (VII), known[7] to be formed from nicotine in rabbit. It is possible that repeated oxidation of VIII or its lactam IX, followed by rearrangement, may proceed in two directions, giving either the tertiary alcohol XIa (probably identical with the "hydroxycotinine" isolated[11] from the dog) which is the cyclic ketal of the known[13] metabolite, γ-3-pyridyl-γ-oxo-N-methylbutyramide (XI), or leading to the methylolamine XX and thence to desmethylcotinine (X).

It is seen that the above simple unified mechanism, depending only on an attack on the α-proton in the rearrangement of the N-oxide, is capable of rationalizing the formation of all known metabolites of nicotine. These predictions have now been tested by carrying out the metal complex catalyzed rearrangement of nicotine N-oxide, using the iron(III)–tartaric acid system at a pH of 6.3, as described[16] for the model system N-*p*-nitrobenzyldimethylamine oxide and for trimethylamine oxide (see ref. 28).



Experimental

Nicotine 1′ oxide[24] was chromatographed on alumina (alkaline, pH 9) and the fraction eluted with 30% methanol in ether was washed with ethyl acetate and solidified in the desiccator. Final purification by vacuum sublimation at 100° (0.01 mm.) gave white hygroscopic crystals, m.p. 172–173° (lit.[25] 172–173°).

Rearrangement of Nicotine N-Oxide with Ferric Ion and Tartaric Acid.—A solution containing 0.001 mole of nicotine N-oxide, 0.003 mole of iron(III) nitrate 9-hydrate, and 0.003 mole of L-(+)-tartaric acid in 15 ml. of water was adjusted to pH 6.3 with a saturated solution of sodium carbonate. The solution was kept for 40 min. in a constant temperature water bath at 80°, after which it was cooled in an ice bath at 5°.

Determination of Formaldehyde.—To the reaction mixture, adjusted to pH 4.7 and chilled to 5°, 161 ml. of 0.4% solution of dimedone in water was added. The solution was shaken vigorously for 10 min. and left aside for 24 hr. The precipitate was filtered, washed with water, and dried to constant weight at 60–70°. The amount of formaldehyde dimedone obtained was 21 mg. (0.00072 mole) (averages of two determinations reproducible to within 1%).

Identification and Determination of the Alkaloidal Products of Rearrangement by Gas Chromatography. A. Gas Chromatographic Conditions.—A U-shaped glass column 2 m. × 5 mm. of 5.6% polyethylene glycol (mol. wt. 20,000) on Firebrick was used, with argon flow 43 ml. per min., input pressure 25 p.s.i., and column temperature 200°.

B. Gas Chromatography of Individual Alkaloids.—A known amount of each of nornicotine, N-methylmyosmine, myosmine, and metanicotine was liberated from its picrate as described.[16] N-Methylmyosmine undergoes rapid decomposition; it was freshly eluted and used immediately; 1% solutions in benzene of the eluted alkaloids were prepared and 10-μl. aliquots were injected. The retention times of the alkaloids are listed in Table I and the separation achieved is shown in Fig. 1.

C. Extraction of Alkaloidal Products from the Reaction Mixture.—A reaction solution (pH 6.3) was cooled to 5°, brought to pH 12 with solid sodium hydroxide, and continuously extracted with benzene for 48 hr. The benzene was evaporated *in vacuo* and a 10% solution of the residue in benzene prepared. This solution was used in the gas chromatography experiments.

D. Gas Chromatography of the Benzene Extract.—In each case, a 50-μl. sample of the benzene extract was injected into the

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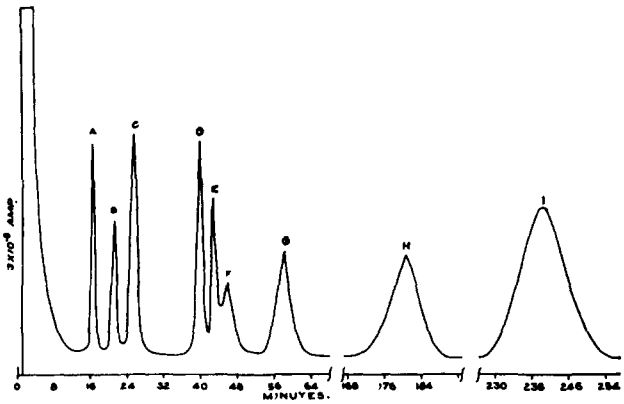

Fig. 1.—Gas chromatographic behavior of nicotine alkaloids; column, 2 m. × 5 mm. 5.6% P.E.G. 20,000 on Firebrick; temperature, 200°; pressure, 25 lb. p.s.i., detector voltage, 800.

Peak	Alkaloid
A	Nicotine (or 3-pyridyl ethyl ketone)
B	3-Pyridyl *n*-propyl ketone
C	N-Methylmyosmine
D	Nornicotine
E	Myosmine (or anabasine)
F	Metanicotine
G	Nicotyrine
H	N-Methylnicotinamide
I	Cotinine

chromatograph. The chromatogram revealed the presence of ten distinct peaks, a typical diagram of which is presented in Fig. 2.

TABLE I

RETENTION TIME OF INDIVIDUAL ALKALOIDS[a]

Alkaloid	Time, min.	Ratio	Quin[b] ratio	Kobashi[c] ratio
3-Pyridyl ethyl ketone	17.28	1.00	1.01	..
3-Pyridyl *n*-propyl ketone	21.92	1.26	1.27	1.24
Nicotine	17.28	1.00	1.00	1.00
N-Methylmyosmine	25.76	1.49	..	..
Nornicotine	39.68	2.30	2.37	2.30
Myosmine	42.88	2.49	2.57	2.47
Anabasine	43.52	2.52	2.65	2.59
Metanicotine	45.92	2.66	3.17	2.87
Nicotyrine	58.88	3.42	3.73	3.47
N-Methylnicotinamide	179.36	10.47	12.3	10.3
Cotinine	239.20	13.84	16.4	14.2

[a] We are grateful to Drs. R. F. Dawson, H. McKennis, L. D. Quin, R. L. Stedman, and E. Wada for reference samples. [b] Ref. 26a reports polyethyleneglycol 20,000 at 190°; nicotine = 5.2 min. [c] Ref. 27a reports polyethylene glycol 6000 at 220°; nicotine = 10.6 min.

E. Quantitative Estimation of the Alkaloidal Products from the Reaction Mixtures.—Generally symmetrical peaks were obtained, and the amount of each alkaloid identified in the benzene extract was calculated against its corresponding standard from the area of the peak. The amount of four unidentified substances was also determined in the same manner, using the nicotine peak as the standard. Table II provides the individual and total amount of the alkaloids in the reaction mixture (average of two determinations, each repeated in triplicate and reproducible to within 5%).

Thin Layer Chromatography.—It was found that myosmine and anabasine had the same retention time and were not separated by gas chromatography. To establish whether peak E in the benzene extract was myosmine or anabasine, thin layer chromatography was used. A plate coated with silica gel G at 250 μ was spotted with 5 μl. of 1% solutions in benzene of nicotine, nornicotine, myosmine, and anabasine, and with 10 μl. of the benzene solution (10%) of the reaction mixture. The plate was developed in a mixture of methanol and chloroform (15:85), and the alkaloids were identified with potassium iodoplatinate spray. In the benzene solution of the reaction mixture, no spot corresponding to anabasine could be detected, indicating the absence of this alkaloid. Spots corresponding to nicotine, nornicotine, and myosmine were all present in the benzene reaction mixture solution. The R_f values were 0.17, 0.29, 0.67, and 0.79 for nornicotine, anabasine, nicotine, and myosmine, respectively. N-Methylmyosmine, nicotyrine, and cotinine were present in too small an amount in the benzene extract to be clearly seen with the Dragendorff spray.

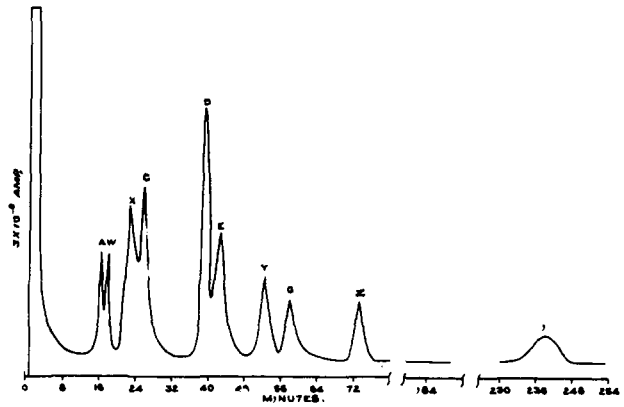

Fig. 2.—Gas chromatogram of benzene extract of nicotine N-oxide reaction mixture; column, 2 m. × 5 mm. 5.6% P.E.G. 20,000 on Firebrick; temperatute, 200°; pressure, 25 lb. p.s.i., detector voltage, 800.

Peak	Alkaloid	Sensitivity
A	Nicotine	1
W	Unidentified	1
X	Unidentified	30
C	N-Methylmyosmine	30
D	Nornicotine	3
E	Myosmine	30
Y	Unidentified	100
G	Nicotyrine	100
Z	Unidentified	100
I	Cotinine	100

TABLE II

AMOUNT OF INDIVIDUAL ALKALOIDS IN THE REACTION PRODUCT

Peak	Retention time ratio	Alkaloid	Weight, %	Amt. per ml. of reacn. prod. soln.,[a] mg.
A	1.00	Nicotine	4.09	3.62
W	1.07	?	4.09	3.62
X	1.35	?	0.96	0.85
C	1.49	N-Methylmyosmine	2.87	2.54
D	2.30	Nornicotine	77.15	68.24
E	2.49	Myosmine	9.50	8.40
Y	3.09	?	0.17	0.15
G	3.42	Nicotyrine	.58	.52
Z	4.28	?	.16	.14
I	13.84	Cotinine	.40	.36

[a] Total amount = 88.44 per ml. of reaction product solution; 180 mg. of nicotine N-oxide gave 130 mg. of crude alkaloidal product from the benzene extract. This was dissolved to make 1.30 ml. of reaction product solution, which therefore contained 115 mg. of total alkaloids isolated.

Results and Discussion

Gas chromatography of nicotine alkaloids has been carried out by Quin[26] and Kobashi,[27] both using polyethylene glycols as the stationary phase. We obtained good separation on 2-m. columns at a column temperature of 200°, as shown in Fig. 1. In the case of myosmine and anabasine, the retention times were so close that separation did not occur on the gas chromatograph. This pair

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of alkaloids was, however, readily separated by thin layer chromatography as described. The retention times of the nicotine alkaloids are shown in Table I, together with the values obtained by Quin[26a] and by Kobashi.[27a] Agreement is remarkably good.

When nicotine N-oxide was submitted to the metal complex catalyzed rearrangement[28] at 80° for 40 min., using the iron(III)–tartaric acid system at pH 6.3, the occurrence of the rearrangement was first shown by the isolation of formaldehyde (as the dimedone derivative). When the reaction mixture was made alkaline and extracted, gas chromatography of the alkaloidal residue revealed the presence of ten peaks, shown in Fig. 2. By comparing the retention times of these peaks with those of the standard alkaloids (Fig. 1), six of the peaks were identified as nicotine, N-methylmyosmine, nornicotine, myosmine, nicotyrine, and cotinine. Peaks W, X, Y, and Z remain unidentified; their retention times are 18.40, 22.88, 53.28, and 73.76 min., respectively. Thin layer chromatography confirmed the identification of nicotine, nornicotine, and myosmine, and the absence of anabasine.

Alkaloids were further identified by supplementing a portion of the reaction mixture extract with the known alkaloid in approximately equal amount, and submitting this to gas chromatography, when only the peak corresponding to that alkaloid would approximately double in height without any change in the retention time. By this means, the following alkaloids were identified in the quantities given in Table II: nicotine, N-methylmyosmine, nornicotine, nicotyrine, and cotinine. No 3-pyridyl ethyl ketone, 3-pyridyl *n*-propyl ketone, metanicotine,[29] anabasine, or anatabine were present. The identification of six nicotine alkaloids from the iron(III)–tartaric acid catalyzed rearrangement of nicotine N-oxide offers strong support for the unified demethylation mechanism outlined above.

It is seen from Table II that 77% by weight of the reaction product was found to be nornicotine. This finding is supported by the isolation of 72% of formaldehyde. Approximately 3% by weight only was identified as N-methylmyosmine. At first sight the preponderance of simple N-demethylation is unexpected, in view of the enhanced acidity of the α-proton adjacent to the pyridine ring, and in view also of the results obtained using N-*p*-nitrobenzyldimethylamine oxide.[13]

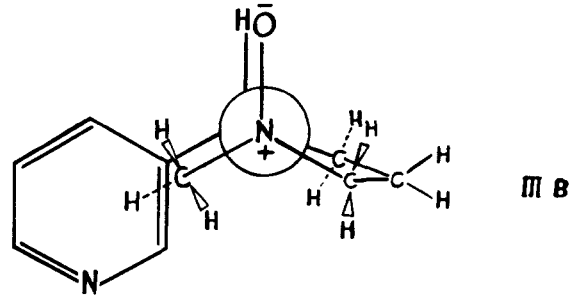
However, the explanation may be found in the stereochemistry of the N-oxide III, which can exist in two possible conformations. From Dreiding models, and drawn in Newman projection, viewed along the axis joining the quaternary (tetrahedral) nitrogen atom to the α-carbon atom adjacent to the pyridine nucleus, form III B has the pyridyl and methyl groups *cis* (eclipsed) to each other, while in form III A it is the N-oxide oxygen which is *cis* (eclipsed) to the pyridine ring.

Stuart–Briegleb models show that in form B the methyl group offers considerable steric hindrance to the *o*-hydrogen atoms of the pyridine ring, so that free rotation is severely restricted. In the other (A) form of the N-oxide, the methyl group and the pyridine nucleus offer the minimum of mutual steric hindrance, and the compound may be expected to exist wholly or predominantly in this form.

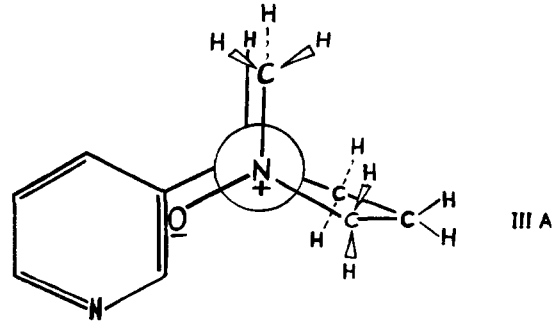
The relative positions (distances and angles) of the methyl hydrogens and the N-oxide oxygen toward each other being unchanged in both isomers, any one of the three methyl hydrogens is available (with free rotation of the methyl group) to form the six-membered ring hydrogen-bonded metal–complex chelate intermediate[28] for the rearrangement by taking up a position *cis* to the oxygen. The formation of the methylolamine, and thence of nornicotine, will therefore not be affected.

In the α-methylene group situated in the pyrrolidine ring, however, only one hydrogen is in a *cis* position to the oxygen in either form A or B, and able to form the chelate ring. Moreover, its acidity will be less than that of the methyl hydrogens because of the adjacent methylene chain.

Finally, the single benzylic hydrogen in form B is *cis* (eclipsed) to the oxygen, and therefore able to give the six-membered metal–complex chelate ring readily, whereas in form A this hydrogen is at a dihedral angle of approximately 120° to oxygen, and is unlikely to be able to form the chelate ring because of the rigidity of the pyrrolidine ring and steric interference by the adjacent pyridyl and methyl groups. As the benzylic hydrogen is by far the most acidic α-hydrogen present, the conclusion would seem that the percentage of N-oxide existing in form B is very small compared with that in form A. Since the N-methyl group in natural (−)-nicotine is likely to be on the opposite, rather than on the same, side of the pyrrolidine ring as the bulky pyridine moiety for steric reasons, it is likely that in the formation of the N-oxide, the oxygen (presumably as OH^+ ion) would attack from below, *i.e.*, at the site of the lone electron pair of the nitrogen, to give form A of the N-oxide. This stereochemical problem is receiving further attention.



III B



III A

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