

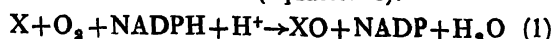
Catalytic *N*-Dealkylation of Tertiary Amines— A Biomimetic Oxygenation Reaction

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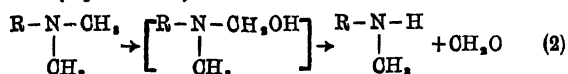
A heterogeneous catalyst system is described for *N*-dealkylation of tertiary amines. A large number of tertiary amines including some important synthetic drugs were *N*-dealkylated to give the corresponding secondary amines in 50-65% yields. The reaction was carried out at room temperature by stirring a solution of a tertiary amine in methanol containing 10% palladium-on-charcoal catalyst. The reaction had absolute requirement for molecular oxygen like the enzymatic dealkylation reaction. It also needed methanol to act as the reductant of molecular oxygen like the NADPH in the enzymatic reaction. A catalytic cycle similar to cytochrome P-450-catalysed oxygenation cycle is proposed for activation and transfer of oxygen to the α -carbon of tertiary amines to give unstable carbinolamines which on dissociation yield secondary amines.

ENZYMATIC *N*-dealkylation of tertiary amines particularly those which are lipid-soluble is a ubiquitous reaction in xenobiotic metabolism. A large number of synthetic drugs, insecticides and carcinogenic amines are known to metabolise by this pathway. *In vitro* experiments have shown that this is an oxidative process catalysed by cytochrome P-450 enzyme system¹ and it has an absolute requirement for both molecular oxygen and NADPH (nicotinamide adenine dinucleotide phosphate in the reduced form), the latter acting as a reductant. Various other types of xenobiotic oxidations, like aromatic hydroxylation, epoxidation, *S*-oxidation and *N*-oxidation are also catalysed by this enzyme system. It is now generally believed² that the primary chemical event in all these oxidations including *N*-dealkylation is the incorporation of one atom of oxygen into the substrate. The other atom of molecular oxygen is reduced to form water (equation 1).



Molecular oxygen becomes activated by binding to the active center of the enzyme in the presence of the substrate to form a ternary complex. The bound oxygen being catalytically active, interacts with the substrate in the complex to form the product.

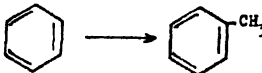

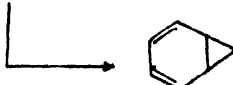
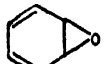
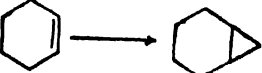

Oxygenation of a tertiary amine at the α -carbon atom would result in an unstable carbinolamine which on dissociation would give a secondary amine (equation 2).



The nature of the so-called 'active' or bound form of oxygen in the above-mentioned complex has been studied extensively. In 1964, Hamilton³ observed the remarkable similarity of many of these enzymatic reactions to the addition reactions

of 'carbenes' and 'nitrenes' (examples in Table 1) and suggested that the active oxygen species was structurally similar to 'carbenes' and 'nitrenes'. It was, therefore, called 'oxene'.

TABLE 1

| Carbenoid reactions | Oxenoid Reactions |
|--|---|
|  |  |
|  |  |
|  |  |
| $R-CH_3 \longrightarrow R-CH_2-CH_3$ | $R-CH_2-CH_2-OH$ Aliphatic Oxidation |

A number of non-enzymatic catalytic systems for aromatic hydroxylation⁴, aliphatic oxidation⁵ and epoxidation⁶ was shown as evidence for the 'oxenoid' mechanism of these reactions. However, no such biomimetic oxidation of tertiary amines with molecular oxygen has been described, although they have been oxidatively dealkylated by a variety of chemical oxidants under different experimental conditions. We now report in this paper that we have discovered a heterogeneous catalyst system for *N*-dealkylation of tertiary amines by oxygenation at room temperature.

The catalytic reaction was carried out at room temperature by stirring a solution of a tertiary

amine in a large volume of methanol containing 10% palladium-on-charcoal catalyst. The course of the reaction was monitored by thin layer chromatography (tlc) and high performance liquid

chromatography (hplc). The hplc profiles of the reactions of some of the tertiary amines at different time intervals are shown in Fig. 1. In most of the cases, the reaction was complete in 24 h. The

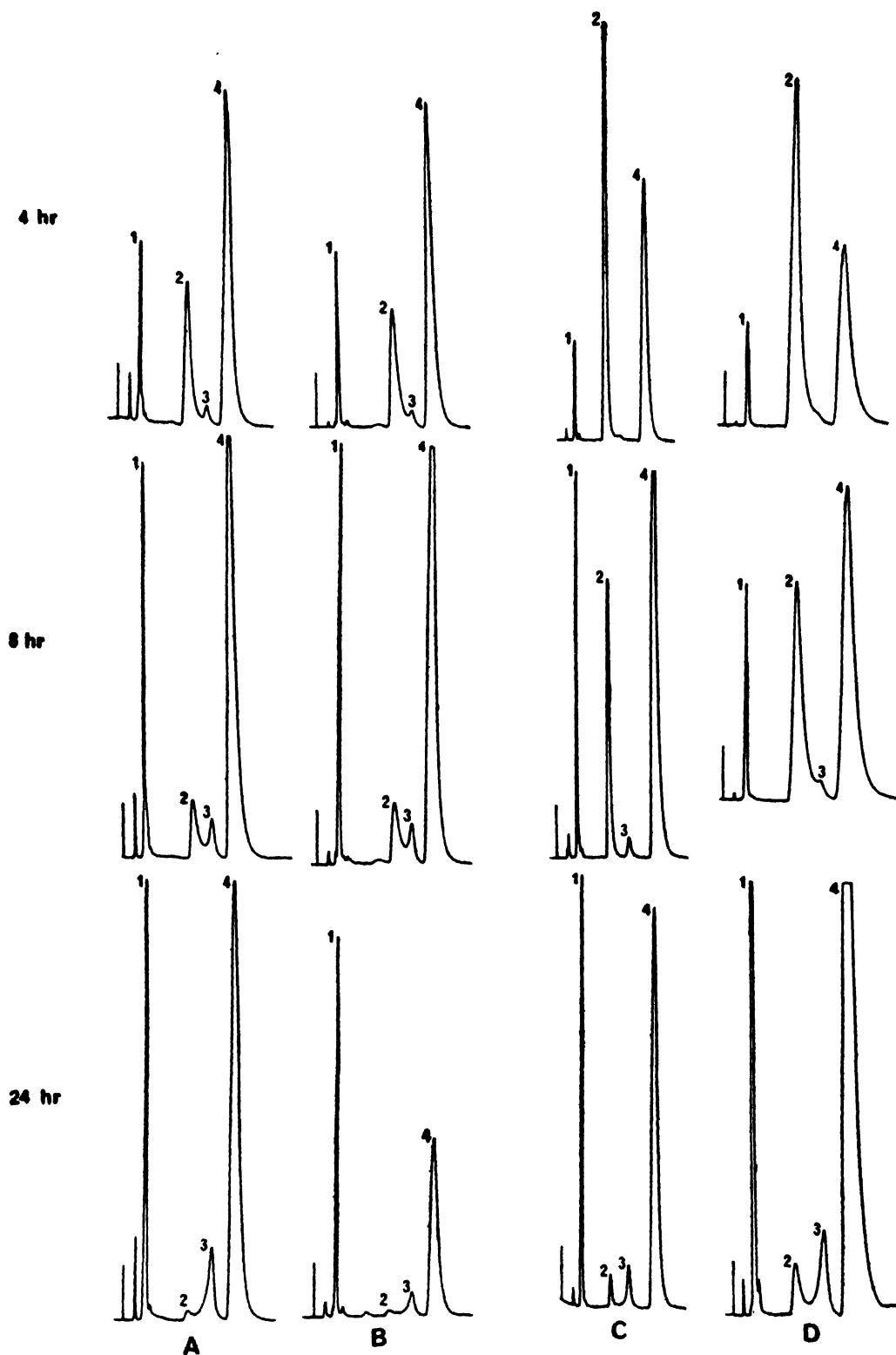


Fig. 1. Hplc profiles of : (A) amitriptyline, (B) imipramine, (C) tripeleonnamine and (D) chlorpromazine.

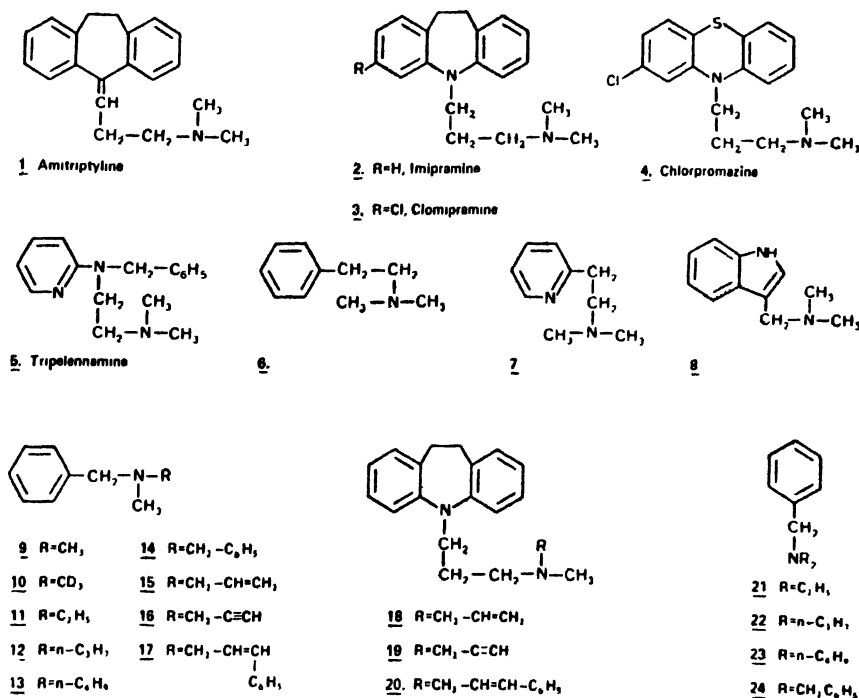
dealkylated products were isolated in pure form, either by column chromatography or by crystallisation of the oxalate salts, in 50-65% yields. The reaction was found to have an absolute requirement for oxygen. However, bubbling of oxygen was not necessary. The reaction was conveniently carried out in the presence of air. When air was excluded or replaced by nitrogen, no reaction occurred. If methanol was replaced by ethanol, the reaction became very slow and it took 3-4 days before any dealkylation could be detected by chromatography. If methanol was substituted by other solvents, like ethyl acetate, dimethylformamide or dioxan, no reaction occurred. Palladium could, however, be substituted by platinum.

Experiments were carried out with a large number of tertiary amines including some very important synthetic drugs which are known to undergo dealkylation on metabolism. Dealkylation occurred with all the compounds in the list except compounds 16, 19, 22, 23 and 24. Compounds 1 to 9, each having two methyl groups, and compounds 10 to 14, each having one methyl group and another alkyl group, underwent demethylation in good yields. Compound 2, having two ethyl groups, underwent deethylation, but no dealkylation occurred with compounds 22, 23 and 24, each having two alkyl groups containing more than two carbon atoms. These results show that oxidation of methyl group was most facile and oxidation of alkyl groups containing more than two carbon atoms did not occur at all. However, the methyl group in compounds 15, 17, 18 and 20 was not oxidised. Instead, the allyl or the substituted allyl

group was oxidised in preference to the methyl group. Cinnamaldehyde was isolated in good yields from reactions of 17 and 20. This result provided direct evidence to support that our catalytic reaction was an oxidative process, and during the oxidation, one alkyl group is lost as the corresponding aldehyde as shown in equation (2). No reaction occurred with compound 16, which is a monoamine oxidase inhibitor, and compound 19. Both these compounds contained a *N*-propargyl group. Neither the methyl nor the propargyl group underwent oxidation. Catalytic oxidation was inhibited by the presence of the *N*-propargyl group.

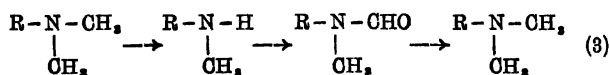
In all the cases studied, no tertiary amine oxide was detected by chromatography at any time during the reaction, nor did any *N*-oxide undergo dealkylation under the experimental condition. This showed that the active oxygen was not transferred to the nitrogen atom to form an *N*-oxide. It was inserted directly into the C-H bond, like a 'carbene'.

In no instance, the reaction proceeded beyond secondary amines to form primary amines. Separate studies with some secondary amines showed that no dealkylation occurred under the reaction condition. Instead, a neutral compound was formed in a small yield after long hours, and considerable amount of polymeric material was formed. Formation of polymers and small amounts of neutral compounds was also observed with tertiary amines (peak No. 1 and peak No. 3 in Fig. 1). The neutral compounds were isolated in several instances and identified by nmr spectroscopy to be

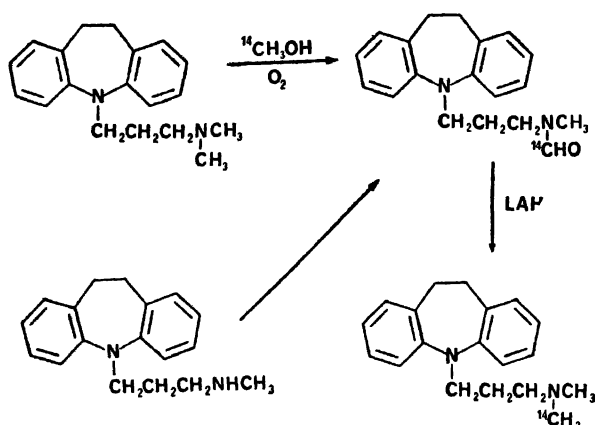


Structures of tertiary amines studied.

N-formyl compounds which could be reduced back to the *N*-CH₃ compounds by treatment with lithium aluminium hydride (equation 3).



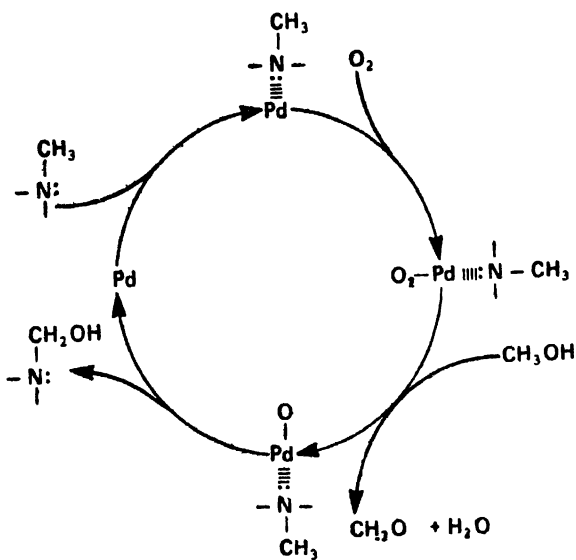
The origin of the formyl group was traced to methanol by carrying out some of these reactions in ¹⁴C-labeled methanol. For example, when the dealkylation of imipramine was carried out in ¹⁴CH₃OH, both the *N*-formyl compound produced, and the tertiary amine prepared from it were radioactive (Scheme 1). The specific activity of



Scheme 1. Neutral product from oxygenation of imipramine and desipramine in ¹⁴CH₃OH.

the pure hydrochloride salt of the tertiary amine thus prepared was same as that of the starting radioactive methanol. These results show that methanol was not only acting as a solvent for the tertiary amine and molecular oxygen, but it was also taking part in the reaction acting as a reductant of one atom of oxygen like NADPH in the enzymatic reaction. Separate blank experiments showed that methanol undergoes catalytic oxidation under the experimental condition to form considerable amount of water, small amount of formaldehyde (detected as the 2,4-dinitrophenylhydrazone derivative) and possibly other one carbon compounds which were, however, not identified. The *N*-formyl compounds were formed by the condensation of the secondary amines with one of the oxidation products of methanol. The only other solvent in which the dealkylation reaction occurred, although to a very small extent, was benzyl alcohol, possibly because it can also act as a reductant like methanol.

All the above results can be explained by assuming a catalytic cycle (Scheme 2), similar to the cytochrome P-450-catalysed reaction. As in the enzymatic reaction, a ternary complex may be formed between palladium, oxygen and a tertiary amine through chemisorption. The ternary complex may then be reduced by methanol to produce an oxenoid intermediate, water, formaldehyde



Scheme 2. Catalytic cycle for oxygenation of tertiary amines.

and other oxidation products of methanol. An oxygen atom is then transferred to the alkyl group which undergoes oxidation.

One further evidence showing the formation of active oxygen under the experimental condition was obtained when it was found that triphenylphosphine was quantitatively oxidised in a few hours to give triphenylphosphine oxide and water.

Experimental

Tlc was carried out on silica gel 60 F-254 (E. Merck) plates of 0.25 mm thickness, and reversed-phase hplc, on a u-Bondapak C₁₈ column with uv detection at 254 nm, using a mixture of methanol and 0.01 M pentane sulphonic acid sodium salt solution in water (75 : 25, v/v) as the mobile phase.

A typical experiment was carried out in the following way. To a solution of a tertiary amine (3 g) in methanol (300 ml), cooled to 0°, was added palladium-on-charcoal (3 g). The mixture was stirred in presence of air at room temperature until the reaction was over. The progress of the reaction was monitored by tlc in methanol-NH₄OH (98 : 2, v/v) and by hplc. The amount of the catalyst was increased by 50% when amines of low molecular weight were used. After the reaction was over, the catalyst was removed by filtration and methanol by distillation. The residue was dissolved in ether. The basic material was separated from the neutral material by extracting the ether solution with 6N HCl solution. The ether solution was used for investigation of the neutral material. The acidic solution was basified and extracted with ether. The ether solution was dried and evaporated to dryness. The residue was then purified either by chromatography on a column of silica gel or by salt formation with oxalic

acid. The oxalate salts of secondary amines were found to be less soluble than those of tertiary amines. Salts were purified by crystallisation from methanol or ether-methanol, and pure amines were generated by basifying. The amines were examined by nmr and mass spectrometry and characterised by comparison with authentic samples. The nmr signals of the alkyl groups of secondary amines usually appeared at a lower field than those of tertiary amines.

The neutral material was purified by chromatography on a column of silica gel and examined by nmr and mass spectroscopy. The *N*-formyl compounds showed the characteristic aldehydic proton peak as a doublet.

The *N*-formyl compounds were reduced by refluxing a solution of the compound in tetrahydrofuran with lithium aluminium hydride. The

reaction products were isolated in the usual way and characterised by tlc, hplc and derivatisation. Radioactive compounds were counted in a liquid scintillation counter, and specific activities per mmol were determined.

References

1. O. HAYAISHI in "Molecular Mechanisms of Oxygen Activation", ed. O. HAYAISHI, Academic Press, New York, 1974, p. 1.
2. W. F. TRAGER, in 'Concepts in Drug Metabolism', eds. P. JENNER and B. TESTA, Marcel Dekker, New York, 1981, Part A, p. 191.
3. G. HAMILTON, *J. Am. Chem. Soc.*, 1964, **86**, 3391.
4. (a) S. UDENFRIEND, C. T. CLARK, J. AXELROD and B. B. BRODIE, *J. Biol. Chem. Soc.*, 1954, **208**, 731; (b) M. VISCONTINI, H. LEIDNER, G. MATTERN and T. OKADA, *Helv. Chim. Acta*, 1966, **49**, 1911.