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THE PHOTOCHEMICAL DEMETHYLATION OF N-METHYL-2,6-DINITRO-4-TRIFLUOROMETHYLANILINE. A POSSIBLE MODEL FOR ENZYMATIC DEALKYLATION

Robert E. McMahon

Lilly Research Laboratories, Indianapolis, Indiana, 46206

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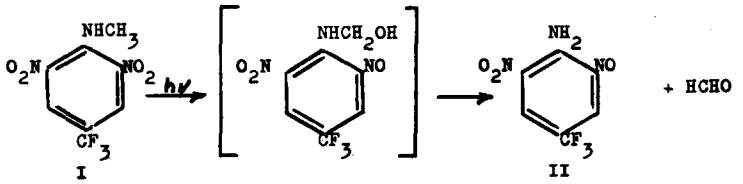
The oxidative dealkylation of N-alkyl amines and amides and of arylalkylethers by enzymes present in the endoplasmic reticulum of hepatic cells (i.e. the "microsomal fraction") is well known. Mechanistically this reaction is best rationalized as a special case of microsomal hydroxylation [1,2]:

$$-\dot{N}-CH_2R \longrightarrow \left[-\dot{N}-CHOHR\right] \longrightarrow -\dot{N}H + O{=}CHR$$

Microsomal hydroxylation appears to be a free radical oxygenation [3] occuring with retention of configuration [4]. It seems likely that in this reaction, membrane itself is an active participant in the reaction, perhaps by binding both substrate and oxygenated enzyme thus serving to bring the centers of reaction into close proximity. The non-enzymatic equivalent of this oxygenation would be an intramolecular oxygen transfer to a saturated carbon atom. An intriguing example of such a reaction is the photochemical conversion of o-nitrobenzhydrylbenzene to diphenyl-o-nitrosophenylcarbinol reported by Tanasecu in 1926 [5]. If this photochemical reaction were a suitable model for microsomal hydroxylation and if dealkylation is a special case of hydroxylation then it seemed that it should be possible to demonstrate the photochemical demethylation of o-nitro-N-methylaniline derivatives. That this reaction would occur seemed

likely from the work of Russell [6] who observed the photochemical degradation of N-2,4-dinitrophenylamino acids. In this communication we now wish to report the photochemically induced N-demethylation of a substituted o-nitro-N-methylaniline as well as the O-demethylation of o-nitroanisole analogs.

N-methyl-2,6-dinitro-4-trifluoromethylaniline , I , (10^{-3} M solution in n-heptane) was irradiated for three hours with a 450 watt high pressure mercury lamp (Hanovia) . Nitrogen was bubbled through the solution during the irradiation. The following reaction was found to occur:



I II

Compound II was recovered and purified by preparative thin layer chromatography on silica gel (solvent system: 98 methylcyclohexane--2 methanol). The product so obtained was crystallized from benzene-heptane mixtures to yield crystals which were green by reflected light and yellow by transmitted light. Since this compound was so difficult to recover and purify, yields of only 5% were realized.(better yields were obtained in later experiments in which methanol was used as a reaction media) . The product had a melting point of 97°-98° and ultraviolet spectrum, λ_{max}^{EtOH} 231 mμ (ϵ 24,000) and 434 mμ(ϵ 7,640) , $\lambda_{max}^{EtOH\ (OH^-)}$ 278 mμ(ϵ 9250), 309 mμ(ϵ 10,000) and 393 mμ(ϵ 17,150). The molecular ion mass found was

235.0176 (calcd. for $C_7H_4F_3N_3O_3$, 235.0205). The infrared spectrum and microanalyses were consistent with the structure proposed.

The formaldehyde that was formed in the reaction was trapped from the nitrogen gas stream in a dry ice cooled trap. It was identified by formation of its dimedon derivative.

The N-propyl analog of I was also irradiated in n-heptane solution and shown to yield II as readily as did compound I. Propionaldehyde was identified as the dimedon derivative and as the 2,4-dinitrophenyl hydrazone.

The work was also extended to demonstrate O-demethylation . For example the 3 hour irradiation of a 10^{-3} M solution of o-nitroanisole in n-heptane led to the formation of formaldehyde in 1% yield as determined by the Nash colorimetric procedure[7]. No formaldehyde was formed when p-nitroanisole was photolyzed , while photolysis of 2,6-dinitroanisole under the same conditions led to a 15% yield of formaldehyde in three hours.

The reactions which are described in this communication are of particular interest since they represent a plausible non-enzymatic model for the important liver microsomal dealkylase reaction. In addition to the relation of this photochemical dealkylation to its enzymatic counterpart, these observations have additional theoretical implications. DeMayo and Reid[8] have suggested a mechanism for the photochemical rearrangement of o-nitrobenzaldehyde to o-nitrosobenzoic acid. Furthermore the DeMayo-Reid mechanism can be applied to other photochemical reactions of aromatic nitro compounds (such as the Tanasescu reaction cited above)[9]. However, the DeMayo-Reid mechanism cannot logically be invoked to explain the dealkyla-

tion reaction since the carbon atom which is oxygenated is not directly attached to the aromatic ring.

Work directed towards a better understanding of the mechanism of this reaction and its relationship to enzymatic dealkylation is now in progress.

REFERENCES

1. R. E. McMahon and N. R. Easton, J. Med. Pharm. Chem. 4, 437 (1961).

2. R. E. McMahon, and H. R. Sullivan, Life Sciences 3, 1167 (1964).

3. The literature on enzymatic dealkylation has recently been reviewed and the arguments which favor a homolytic mechanism cited, cf. R.E.McMahon, J. Pharm Sci. in press.

4. E. J. Corey and G. A. Gregoriou, J. Am. Chem. Soc. 81, 3127 (1959).

5. I. Tanasescu, Bull. Soc. Chim. France 39, 1454 (1926).

6. D. W. Russell, J. Chem. Soc. 894 (1963).

7. J. Cochin and J. Axelrod, J. Pharmacol. 125, 105 (1959).

8. P. DeMayo and S. T. Reid, Quart. Revs. 15, 393 (1961).

9. M. L. Scheinbaum, PhD Dissertation, Harvard University, 1964.