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Photochemical Oxidation of Nicotine in the Presence of Methylene Blue

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The photochemical oxidation of nicotine in the presence of methylene blue produces a compound which has not been completely characterized. During the course of this investigation, it was learned that a similar, if not identical, product had been isolated by W. G. Frankenburg (*1*) from the alkaloids of fermented tobacco. It was therefore deemed advisable to disclose our findings simultaneously.

If an aqueous solution of *l*-nicotine is irradiated in the presence of oxygen and a small amount of methylene blue, a rapid oxidation of the nicotine takes place which, in the dark, comes to a standstill. The effective wave length (around 6,700 A) coincides with the maximum absorption of the dye, and thus the "light-excited" dye can serve as a hydrogen acceptor, as shown by its rapid bleaching. The leuco methylene blue formed is reoxidized and serves continuously as a hydrogen acceptor. The oxygen required for the reoxidation of the reduced dye or, in terms of total effect, for the oxidation of nicotine thus serves as a means to follow the rate of the reaction.

An adaptation of the manometric technique of Warburg and Negelein (*3*) was used. White light of high intensity was passed horizontally through the glass wall of the water bath and reflected on the bottom of the vessel by a mirror placed at 45° under the respirometers. In general, 20 mg of the compound to be studied was dis-

solved in 1.5 cc of water and placed in the main chamber, and 0.5 cc of water solution of methylene blue containing 0.1 mg was placed in the side arm. After the vessel was filled with oxygen and the dye dumped into the main chamber, the oxygen uptake was measured in the usual fashion at the desired water-bath temperature. A rapid oxygen uptake took place which stopped sharply after about 4 hrs at 40°, when an equimolar amount of oxygen had been taken up. The optimum pH for the oxygen uptake was about 9. There was no CO_2 evolution.

Irradiation experiments under anaerobic condition in Thunberg tubes, to prevent reoxidation of the leuco dye, showed that the bleaching time is practically not affected at temperatures of 30°, 40°, 50°, 60°, and 70°, thus indicating a true photochemical reaction in this phase. The reaction appeared to be reversible, although it proceeded slowly, as in the thionine-iron system (*2*, *4*, *5*). The aerobic photo-oxidation of nicotine, however, is strongly accelerated by increasing temperature, which would indicate the participation of a dark reaction in addition to the previously observed light-sensitive reaction.

The N—CH_3 group of the pyrrolidine ring seems to be important in the reaction, since under similar conditions *d,l*-nornicotine[2] acts sluggishly. Pyridine, β-picoline, β-vinylpyridine, nicotinic acid, and nicotinamide are unreactive. N—CH_3-pyrrolidine, however, which is a part of the nicotine molecule, is photo-oxidized in the presence of the dye at the same rate and to the same extent as nicotine itself. These experiments indicate that the chemical changes due to the irradiation are confined to the N—CH_3-pyrrolidine ring.

The product (obtained by larger-scale experiments) is a yellow viscous oil, not volatile in steam, practically insoluble in ether, but soluble in chloroform, in polar solvents, and in water. It is optically active ($\alpha_D^{20} = -35.2°$), indicating that the asymmetric carbon atom is not involved in the reaction. During the irradiation, the pH of the reaction mixture dropped from 10.4 to 6.8, suggesting that the strongly basic pyrrolidine nitrogen is involved in the reaction by forming, for example, an amine oxide. The elementary analysis of the ether-insoluble

irradiation product of nicotine was: Calculated for $C_{10}H_{14}N_2O_2$: C, 61.85%; H, 7.21%; N, 14.43%; Found: C, 62.69%; H, 7.21%; N, 14.08%. Upon reduction with Zn and acetic acid in alcoholic solution, it was to a large part reconverted into nicotine (85–100%). Qualitative tests for aldehyde, keto, peroxide, and alcoholic groups were negative. The compound is not identical with oxy-nicotine. Further work is in progress to identify the product, but in the meantime, the following over-all equations are proposed for the reaction:

$$\text{(I)}\quad C_{10}H_{14}N_2 + M{-}B^{*} \xrightarrow{\text{light}} C_{10}H_{12}N_2 + M{-}B(H_2)^{\dagger}$$

$$\text{(II)}\quad M{-}B(H_2) + O_2 \longrightarrow M{-}B + H_2O_2$$

$$\text{(III)}\quad C_{10}H_{12}N_2 + H_2O_2 \longrightarrow C_{10}H_{14}N_2O_2$$

* Methylene blue

† Leuco methylene blue

Reaction I would represent the light reactions; II and III, the dark ones. An attempt to demonstrate the intermediate formation of H_2O_2, as required by reaction II, was not successful. Preliminary work indicated that the failure might be due to the high reactivity of certain tertiary amines with nascent H_2O_2.