Tetrahedron Letters No.32, pp. 3843-3846, 1966. Pergamon Press Ltd.
Printed in Great Britain.

Photochemistry IV[1]. A Photodeamination

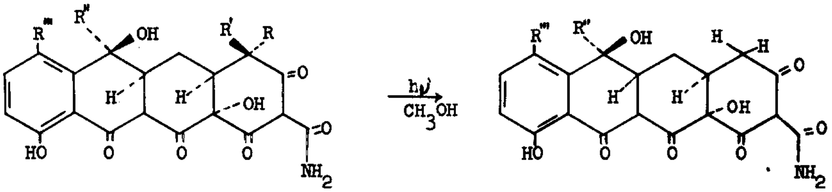
Joseph J. Hlavka and Panayota Bitha

Organic Chemical Research Section,
Lederle Laboratories Division of American Cyanamid Company,
Pearl River, New York

(Received 7 June 1966)

We wish to report on a novel photochemical reaction in the tetracycline series. We have found that irradiation of a solution of tetracycline (I) and a sensitizer[2] in methanol through quartz glass[3] with two 100-watt mercury arc lamps[4] results in a selective carbon-nitrogen bond scission to yield 4-dedimethylaminotetracycline (VII)[5]. Similar photodeaminations were obtained with the related compounds II, III, IV[6] and V. Alternatively the reaction will proceed without a sensitizer when a 450-watt lamp[4] is used.

Table I



I - VI

VII - X

I, R = $N(CH_3)_2$, R' = R''' = H, R'' = CH_3 ⟶ VII, R'' = CH_3, R''' = H

II, R = $N(CH_3)_2$, R' = H, R'' = CH_3, R''' = Cl ⟶ VIII, R'' = CH_3, R''' = Cl

III, R = $N(CH_3)_2$, R' = R'' = H, R''' = Cl ⟶ IX, R'' = H, R''' = Cl

IV[6], R = $N(C_2H_5)(CH_3)$, R' = R'' = R''' = H ⟶

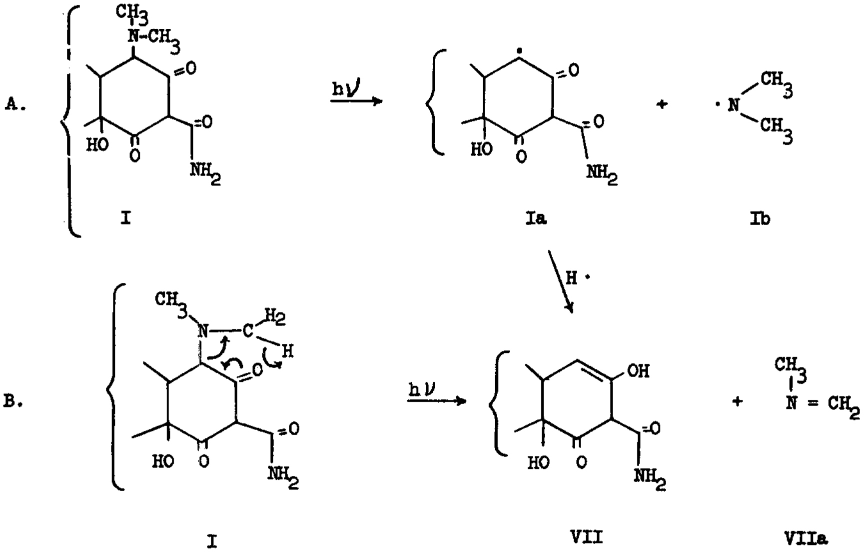
X, R'' = R''' = H.

V, R = $N(CH_3)_2$, R' = R'' = R''' = H ⟶

VI, R' = $N(CH_3)_2$, R = R'' = H, R''' = Cl $\not\longrightarrow$

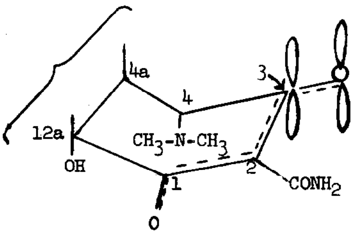
The stereochemical and electronic requirements for this reaction were partially defined by the failure of both 7-chloro-6-demethyl-4-epitetracycline (VI) and tetracycline hydrochloride (I + HCl) to undergo the elimination.

This photochemical reaction appears to be unique and two pathways have been considered for this elimination. In pathway A. the photochemically excited carbonyl system[7a,b] would undergo the deamination with the formation of radicals Ia and Ib which could either recombine or abstract hydrogen from the solvent to yield 4-dedimethylaminotetracycline (VII)and dimethylamine. In B the photochemically excited ketone abstracts a hydrogen[8] from the dimethylamino side chain in a concerted manner to yield VII and the Schiff base VIIa which on hydrolytic work-up would give methylamine.

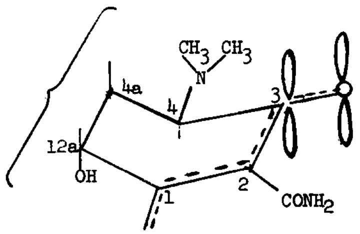


The volatile amine product has been collected, converted to the 3,5-dinitrobenzamide derivative and compared via thin layer chromatography to both N, N-dimethyl-3,5-dinitrobenzamide and N-methyl-3,5-dinitrobenzamide. It proved to be identical to the N, N-dimethyl derivative and therefore supports the non-concerted process A.

Recent x-ray studies[9] have shown that the conformational requirements about the C(4) - C(4a) atoms of a natural tetracycline, i.e. II •HCl, imposed by the planarity of the C(1), C(2) and C(3) atoms would place the dimethylamino group in a pseudo axial position of the ring. The selectivity of this photodeamination may be due to the difference in conformation between the 4-epi and natural tetracyclines so that in the natural series the carbon-nitrogen bond at C(4) is more nearly perpendicular to the C(1), C(2) and C(3) plane, II, and would allow for maximum overlap in the transition state between the sigma electrons of the C(4) axial bond and the pi electrons of the carbonyl function at C(3). However with the dimethylamino group in the equatorial position, IIa, there would be less orbital overlap with the C(3) oxygen. Such an equatorial arrangement could explain the un-reactivity of the epi compound to the photolytic conditions.



II



IIa

ACKNOWLEDGEMENTS

We are especially grateful to Mr. C. Pidacks and his staff for the isolation and identification of the volatile amine fragments. We also wish to thank Mr. W. Fulmor and Mr. G. Morton for the n.m.r. spectra, Mr. L. Brancone and staff for the analytical data and finally we are indebted to Professor H. Zimmerman, University of Wisconsin and Dr. A. Kende for many stimulating discussions.

REFERENCES

1. Paper III: J. Hlavka, Chemistry and Industry, 34, 1500 (1965).

2. Both acetophenone and benzophenone were used.

3. The reactions were carried out in a water-cooled Hanovia quartz vessel obtained from the Hanovia Lamp Division, Newark, New Jersey.

4. The lamps were obtained from the Hanovia Lamp Division, Newark, New Jersey. The 100-watt lamps were type 30620 and the 450-watt lamp was type 7420.

5. J.R.D. McCormick, et al., J. Am. Chem. Soc., 79, 2849 (1957).

6. R. C. Esse, J. A. Lowery, C. R. Tamorria and G. Sieger, J. Am. Chem. Soc., 86, 3877 (1964).

7a. A. Blacet and F. Strachan, J. Am. Chem. Soc., 77, 5254 (1955). These authors have reported on the beta-elimination of a halogen atom in the photolysis of chloroacetone.

b. A. Padwa and R. Layton, Tetrahedron Letters, 2167 (1965). These authors obtained a beta-elimination during the photolysis of α-diazoacetophenone.

8. S. Levine and M. C. Wani, J. Org. Chem., 30, 3185 (1965).

9. J. Donohue, et al., J. Am. Chem. Soc., 85, 851 (1963).