Anal. Calcd. for C_8H_4SFBr: C, 41.56; H, 1.73; S, 13.85; F, 8.23; Br, 34.63. Found: C, 41.65; H, 1.86; S, 13.78; F, 8.23, 8.26; Br, 34.27, 34.35.

2-Fluoro-3-thianaphthenecarboxylic Acid—To 1.47 g. (0.023 mole) of *n*-butyllithium dissolved in 3 ml. of anhydrous ether was added, under a nitrogen atmosphere at −70°, a solution of 5.34 g. (0.023 mole) of 3-bromo-2-fluorothianaphthene dissolved in 5.0 ml. of anhydrous ether during 5 min. The reaction mixture was then poured rapidly over a Dry Ice–ether slurry and allowed to warm to room temperature. The ether solution was extracted with 25 ml. of water followed by two 50-ml. portions of a 5% aqueous sodium hydroxide solution. The aqueous extracts were combined, boiled to remove the ether, cooled, and acidified with concentrated hydrochloric acid. The white precipitate which formed on acidification was recovered by filtration and washed with water. It was crystallized three times from a minimum of 95% ethanol to afford 2.5 g. (0.0127 mole; 55%) of fine white needles which had a melting point of 188–188.5°.

Anal. Calcd. for $C_9H_5O_2SF$: C, 55.10; H, 2.55; S, 16.33; F, 9.69. Found: C, 54.94; H, 2.60; S, 16.49; F, 9.48, 9.46.

Perchlorylbenzene—A solution of phenyllithium, 0.1 mole, in 50 ml. of anhydrous ether was prepared according to Gilman's[6] procedure and treated with perchloryl fluoride in the manner already described. Product isolation, by procedures discussed before and vacuum distillation of the crude product gave 1.8 g. (0.011 mole, 11.0%) of perchlorylbenzene, b.p. 78–79° (2 mm.) as identified by infrared spectra.[7]

Acknowledgment.—This research was supported in part by a financial grant from American Cancer Society.

(6) H. Gilman, *Org. Reactions*, **8**, 286 1954.

(7) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 5286 (1958).

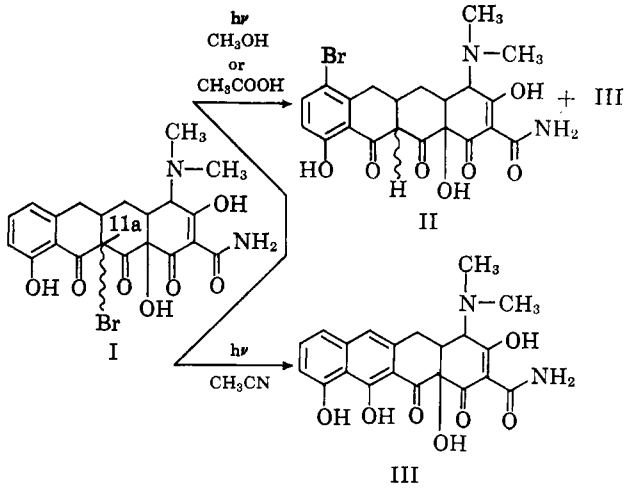
The 6-Deoxytetracyclines.[1] VI. A Photochemical Transformation

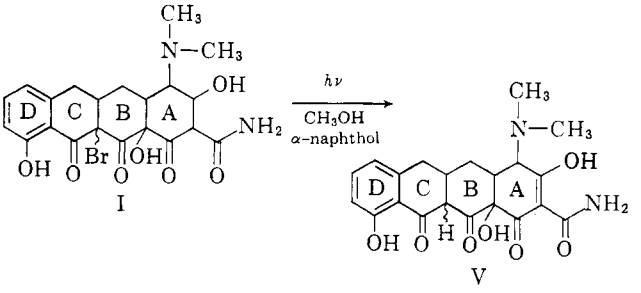
JOSEPH J. HLAVKA AND HELEN M. KRAZINSKI

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

Received December 26, 1962

We have found that photolysis of 11a-bromo-6-demethyl-6-deoxytetracycline[2] (I) in either methanol or glacial acetic acid yields primarily 7-bromo-6-demethyl-6-deoxytetracycline[3] (II) and, as a minor component, 6-demethylanhydrotetracycline[4] (III). The remarkable selectivity of this photorearrangement indicated, at first, an intramolecular mechanism. In order to elucidate the reaction path, the bromo compound, I, was irradiated in the presence of α-naphthol. Under these conditions very little (<10%) brominated tetracycline (II) was obtained, the major product being 6-demethyl-6-deoxytetracycline[5] (V). The isolation of V establishes the intermolecular pathway of the reaction, the α-naphthol acting as a scavenger for the bromine atom produced during irradiation.





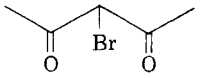
When the photolysis was run in acetonitrile, there was no aromatic bromination only dehydrohalogenation *via* 5a,11a to give 6-demethylanhydrotetracycline[4a,b] (III). Similarly the small amount of anhydro material[4a] (III) obtained from methanol or acetic acid is due to this (competing) dehydrohalogenation *via* 5a,11a.

Whatever the initial excited state(s) of the α-bromodicarbonyl system, there is probably an eventual formation of a substituted hypobromite (CH_3OBr when methanol is the solvent or CH_3COOBr when acetic acid is the solvent) which acts as a selective electrophilic brominating agent[6] to yield the 7-halo product, II. This intermediate hypobromite may result from either nucleophilic attack of the solvent (in the case of methanol or acetic acid) on a photoactivated carbon–halogen bond (Ia) to give the substituted hypobromite, Ib, as shown in Chart I, or from a stepwise process initiated by light-induced elimination of hydrogen bromide which in turn participates in the reaction sequence given in Chart II.

The report[7] that bromine in methanol does participate in an equilibrium with the formation of methyl

(1) For the previous paper in this series, see J. J. Hlavka, H. Krazinski, and J. H. Boothe, *J. Org. Chem.*, **27**, 3674 (1962).

(2) J. J. Hlavka, A. Schneller, H. Krazinski, and J. H. Boothe, *J. Am. Chem. Soc.*, **84**, 1426 (1962).

(3) This photo rearranged product (II) still contains bromine but no longer has the bromo system  as evidenced by the lack of a positive starch iodide test and the absence of the isolated carbonyl (at carbon 12) stretching at 1739 cm.$^{-1}$ in the infrared. In addition this material was compared by infrared, ultraviolet, and paper strip chromatography in four different systems to authentic material.[2] It was identical in all cases.

(4) (a) An authentic sample of this material was prepared by treating [see J. Webb, R. Broschard, D. Cosulich, W. Stein, and C. Wolf, *ibid.*, **79**, 4563 (1957)] 6-demethyltetracycline with concentrated hydrochloric acid. This authentic sample was identical to the photo-product (III) in all respects, *i.e.*, ultraviolet, infrared, and paper strip chromatography in different solvent systems. (b) This type of dehydrohalogenation was reported by D. Kevill and N. Cromwell, *J. Am. Chem. Soc.*, **83**, 3812 (1961). They found that α-halo ketones undergo facile elimination reactions in acetonitrile using a variety of catalysts.

(5) (a) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *ibid.*, **82**, 3381 (1961); (b) C. R. Stephens, *et al.*, *ibid.*, **80**, 5324 (1958).

(6) We have found previously (see ref. 2) that electrophilic halogenation in concentrated sulfuric acid gave exclusively the 7-halo isomer.

(7) R. Meinel, *Ann.*, **510**, 129 (1934); **516**, 237 (1935).

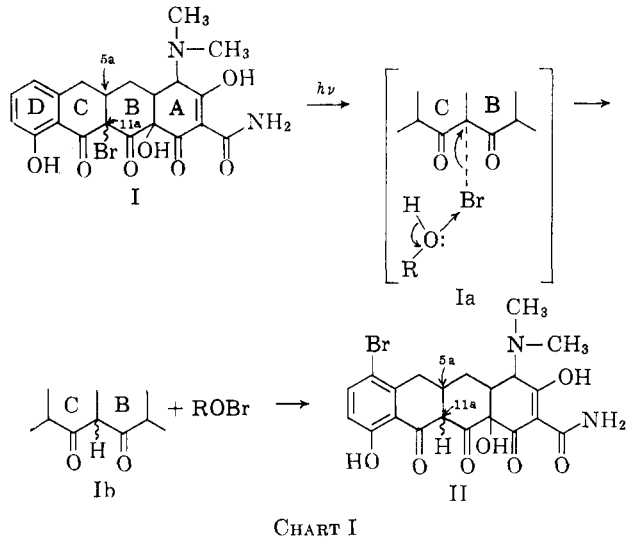


CHART I

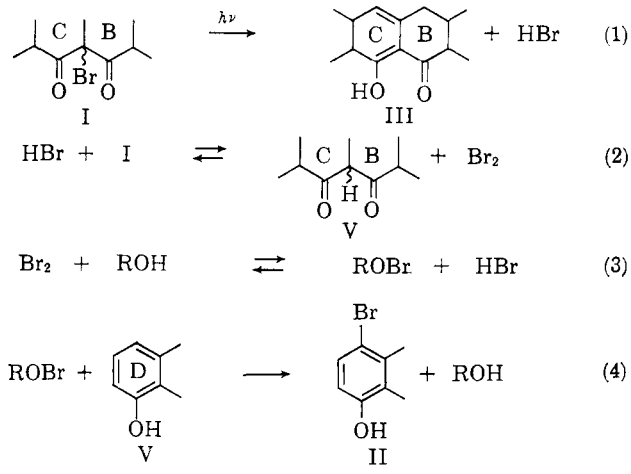


CHART II

hypobromite, prompted us to treat 6-demethyl-6-deoxytetracycline (V) with a bromine–methanol solution. Analysis of the reaction mixture by paper chromatography in a number of different solvent systems showed both 11a and 7-substituted products. In contrast, reaction of 6-demethyl-6-deoxytetracycline with bromine in the nonhydroxylic solvent, 1,2-dimethoxyethane, yielded no 7-halo derivative. These experimental results lend support to our suggestion that a transient hypobromite may be the effective halogenation agent in our photochemical process, but do not differentiate between the two alternative reaction pathways illustrated in Chart I and II. The mechanism in Chart II is consistent with the observed action of methanolic hydrogen bromide (in the dark) upon I. Examination of the reaction products by paper chromatography (four different systems) showed a small amount of the starting material and approximately equal amounts of II and V. The exact nature of hypobromite formation is under investigation.

Since both the preparation of the 11a bromo derivative, I, and the irradiations are carried out under mild conditions,[8] this reaction sequence provides a simple and convenient method for obtaining active halogen derivatives[2] in th 6-deoxytetracycline series.

(8) The previous method[2] involved the use of large quantities of concentrated sulfuric acid which resulted in rather tedious isolation procedures.

Experimental[9,10a]

General Procedure for Irradiation of 11a-Bromo-6-demethyl-6-deoxytetracycline Hydrochloride (I).—A solution of 100 mg. (0.19 mmole) of 11a-bromo-6-demethyl-6-deoxytetracycline hydrochloride in 50 ml. of solvent[11] was irradiated for 4 hr. in a double-walled immersion well.[10b] When either methanol or acetonitrile was used as the solvent, the reaction mixture was evaporated to dryness *in vacuo*. In the case of acetic acid the solvent was lyophilized.

The reaction product obtained from acetonitrile was pure enough to compare to an authentic sample of 6-demethylanhydrotetracycline.[4a]

The reaction product obtained from methanol or acetic acid was purified by partition column chromatography. The reaction product was dissolved in 15 ml. of the lower phase of the solvent system heptane–ethyl acetate–methanol–water (70:30:12:8) and 30 g. of Celite[12] was added to the solution. The mixture was placed on top of a column prepared from 300 g. of Celite which had been mixed with 50 ml. of the lower phase of the solvent system. The column [hold-back volume (h.b.v.)[13], 464 ml.] was eluted with the upper phase of the solvent system and the effluent was passed through a recording spectrophotometer (set at 265 mμ). There were two major peaks, the first occurring at 0.7 h.b.v. and the second at 2.2 h.b.v. The first peak was evaporated to dryness and the residue obtained was identical in all respects to 6-demethylanhydrotetracycline[4] (10% yield), the second peak after evaporation of the solvent was identical in all respects to 7-bromo-6-demethyl-6-deoxytetracycline[3] (90% yield).

Photolysis of 11a-Bromo-6-demethyl-6-deoxytetracycline Hydrochloride (I) in the Presence of α-Naphthol.—A solution of 100 mg. of I and 90 mg. of α-naphthol in 15 ml. of methanol was irradiated for 4 hr. in a double-walled immersion well.[10b] The methanolic solution was evaporated to a volume of 2 ml. and diluted with 100 ml. of ether. The solid weighed 90 mg. This material was separated by fractional crystallization from methanol/ether. Paper strip chromatography showed the main fraction (90%) to be 6-demethyl-6-deoxytetracycline[5] and second fraction (10%) to be 7-bromo-6-demethyl-6-deoxytetracycline.[2,3]

Reaction of 6-Demethyl-6-deoxytetracycline with Bromine.—(1) A solution of 0.1 g. (0.24 mmole) of 6-demethyl-6-deoxytetracycline (free base) and 0.48 mmole of bromine in 0.75 ml. of methanol and 5 ml. of methylene chloride was stirred at room temperature for 2 hr. The solvents were evaporated *in vacuo* and the residue was dissolved in 2 ml. of methanol. This solution on dilution with ethyl ether yielded 90 mg. of solid.

Analysis of this reaction product by paper chromatography in five different solvent systems[14] as well as infrared and ultraviolet spectra showed both 7-bromo-6-demethyl-6-deoxytetracycline[3] (10%) and 11a-bromo-6-demethyl-6-deoxytetracycline[2] (90%) were formed.

(2) To a solution of 0.10 g. (0.24 mmole) of 6-demethyl-6-deoxytetracycline in 15 ml. of 1,2-dimethoxyethane was added 0.05 ml. (1.00 mmole) of liquid bromine. The solution was stirred at room temperature for 3 hr. and the solvent evaporated to dryness *in vacuo*. The residue was dissolved in a minimum amount of methanol and added to ethyl ether. The product that separated was identical in all respects to 11a-bromo-6-demethyl-6-deoxytetracycline[2] (*i.e.*, infrared and ultraviolet spectra and R_f values in the system butanol–phosphate, pH 2).

(9) We are indebted to C. Pidacks and co-workers for the purification of reaction products and to Miss Ruth Livant for paper chromatographic results.

(10) (a) All irradiations were carried out using a Hanovia lamp, Model #30,600, obtained from the Hanovia Lamp Division, Newark, N. J. (b) This reaction vessel was also obtained from the Hanovia Lamp Division.

(11) The solvents used were methanol, acetic acid, and acetonitrile.

(12) Celite is the trademark of the Johns-Manville Corp. for diatomaceous earth products.

(13) Hold-back volume is the volume of solvent necessary to fill the packed column.

(14) The solvent systems used were: (1) phosphate–versene, pH 3; (2) butanol–phosphate, pH 2; (3) isobutanol–isobutylacetate–versene, pH 7.7; (4) ethyl acetate; (5) nitromethane–benzene–pyridine, pH 3.4.