Notes

The 6-Deoxytetracyclines. IV. A Photochemical Displacement of a Diazonium Group[1]

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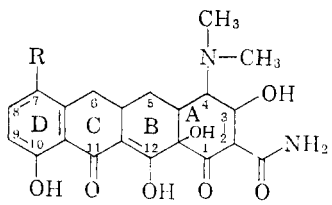
The availability of 6-demethyl-6-deoxytetracycline-7-diazonium sulfate hydrochloride (II)[1] has permitted for the first time a number of photoinduced substitution reactions in the tetracycline series. We have found that photolysis of 6-demethyl-6-deoxytetracycline-7-diazonium sulfate hydrochloride in acetic acid for five hours yields



I. R = H
II. R = $N\equiv N^+$—
III. R = Cl
IV. R = $OCOCH_3$
V. R = OCOH
VI. R = OH
VII. R = F
VIII. R = Br
IX. R = I

the previously described 7-chloro-6-demethyl-6-deoxytetracycline[2] (III) and 6-demethyl-6-deoxytetracycline[3] (I) as well as the heretofore unknown 7-acetoxy-6-demethyl-6-deoxytetracycline (IV). When formic acid was used as a solvent in this photodecomposition, the 7-formyloxy derivative (V) was isolated as the principal reaction product.

Hydrolysis of either the 7-acetoxy (IV) or the 7-formyloxy (V) derivative yields the same hydroxy compound, VI. In the case of 6-demethyl-6-deoxy-7-formyloxytetracycline, hydrolysis occurred during column chromatography giving the pure 7-hydroxy derivative (VI).

Although the synthesis of 7-bromo-6-demethyl-6-deoxytetracycline[1] (VIII) and 7-iodo-6-demethyl-6-deoxytetracycline[1] (IX) has been accomplished, the preparation of the 7-fluoro derivative, by conventional pathways, has until now eluded us. An attempted Schiemann reaction on the diazonium fluoroborate yielded nontetracycline products. Photodecomposition of the 6-demethyl-6-deoxytetracycline diazonium fluoroborate in acetic acid, on the other hand, yielded the desired 7-fluoro derivative (VII) along with some 7-acetoxy compound (IV) and 6-demethyl-6-deoxytetracycline (I). The use of photolysis in this decomposition obviates the use of high temperature and protected aromatic hydroxyl groupings which are standard techniques for the formation of fluorophenols by the general Schiemann reaction.

Recently,[4] Lee and his co-workers have suggested two alternative pathways for the decomposition of a diazonium salt depending on the solvent used. They reported that in ethanol the photodecomposition of a diazonium salt occurs *via* a radical intermediate while in water an ionic process predominates. They found the photodecomposition of a nitrobenzenediazonium chloride in water yielded both a nitrophenol and a chloronitrobenzene. In ethanol, on the other hand, the major product of photolysis was the reduction product, nitrobenzene.

In a mixture of acetic acid and water we have obtained, in addition to the reduced product 6-demethyl-6-deoxytetracycline, a 7-halo and a 7-acetoxy derivative in a ratio of 1:1:2. The isolation of these products would be consistent with either a homolytic and heterolytic process operating simultaneously or possibly a radical cation intermediate as proposed by Taft[5] for the thermal decomposition of a diazonium salt.

The relative *in vitro* antibacterial activities of the compounds discussed above are given in Table I.

Experimental[6,7]

7-Acetoxy-6-demethyl-6-deoxytetracycline (IV).[8,9]—A solution of 1.0 g. (1.75 mmoles) of 6-demethyl-6-deoxytetracycline-7-diazonium hydrochloride sulfate in 3.0 ml. of water and 250 ml. of glacial acetic acid was irradiated at room temperature for 5 hr.

The reaction mixture was lyophilized and the tan residue slurried in ethyl ether, filtered, and dried. This material was purified by partition column chromatography[10] using a solvent system chloroform (40)–butanol (1)–0.2 *M* phos-

(1) This paper is part of a series in the tetracycline field. For the previous paper in this series see J. Hlavka, A. Schneller, H. Krazinski, and J. Boothe, *J. Am. Chem. Soc.*, **84**, 1426 (1962).

(2) J. R. D. McCormick and E. R. Jensen, German Patent 1,082,905, June 9, 1960.

(3) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **82**, 3381 (1960).

(4) W. E. Lee, J. G. Calvert, and E. W. Malmberg, *ibid.*, **83**, 1931 (1961).

(5) R. W. Taft, *ibid.*, **83**, 3350 (1961).

(6) We are indebted to C. A. Pidacks and co-workers for the separation of the reaction products by partition column chromatography and to L. Brancone and staff for the analytical data.

(7) All irradiations described were carried out using a Hanovia lamp, Model #30,600, obtained from The Hanovia Lamp Division, Newark, N. J.

TABLE I

In Vitro ACTIVITIES IN % COMPARED TO TETRACYCLINE[a]

Tetracycline	100
6-Demethyl-6-deoxytetracycline (I)	160
6-Demethyl-6-deoxytetracycline-7-diazonium sulfate hydrochloride (II)	20
7-Chloro-6-demethyl-6-deoxytetracycline[b] (III)	300
7-Acetoxy-6-demethyl-6-deoxytetracycline (IV)	120
6-Demethyl-6-deoxy-7-formyloxytetracycline (V)	32
6-Demethyl-6-deoxy-7-hydroxytetracycline (VI)	23
6-Demethyl-6-deoxy-7-fluorotetracycline (VII)	220
7-Bromo-6-demethyl-6-deoxytetracycline (VIII)	200
6-Demethyl-6-deoxy-7-iodotetracycline (IX)	120

[a] Activities were measured turbidimetrically against *Staph. aureus* by the method of E. Pelcak and A. Dornbush, *Ann. N. Y. Acad. Sci.*, **51**, 218 (1948). [b] See ref. 2.

phate buffer, pH 2.0 (20); $[\alpha]^{25}D$ −98°; R_f 0.68; $\lambda_{max.}^{0.1\ N\ HCl}$ 348, 265 mμ; log ε 4.55, 4.72.

Anal. Calcd. for $C_{23}H_{24}O_9N_2$: C, 58.5; H, 5.1; OAc, 9.1. Found: C, 58.3; H, 5.7; OAc, 9.0.

In addition to the 7-acetoxy derivative (IV), we obtained some 7-chloro-6-demethyl-6-deoxytetracycline[2] (III) and some 6-demethyl-6-deoxytetracycline[3] (I) in a ratio of 2:1:1, respectively.

6-Demethyl-6-deoxy-7-hydroxytetracycline (VI).[8,9]—A solution of 0.075 g. (0.159 mmole) of 7-acetoxy-6-demethyl-6-deoxytetracycline in 0.30 ml.of 1 *N* sodium hydroxide was stirred at room temperature for 5 min. The solution was acidified with hydrochloric acid to pH 4.5 and the precipitate was collected by filtration, washed with water, and dried *in vacuo* at room temperature, yield 20 mg. $[\alpha]^{25}D$ −171°; R_f 0.58; $\lambda_{max.}^{0.1\ N\ HCl}$ 340, 282 mμ; log ε 3.89, 4.85.

Anal. Calcd. for $C_{21}H_{22}N_2O_8 \cdot H_2O$: C, 56.4; H, 5.4; N, 5.2. Found: C, 56.7; H, 5.8; N, 5.1.

6-Demethyl-6-deoxy-7-formyloxytetracycline Sulfate (V).—A solution of 0.30 g. (0.523 mmole) of 6-demethyl-6-deoxytetracycline-7-diazonium hydrochloride sulfate in 40 ml. of 98% formic acid was irradiated for 3 hr. at room temperature. The formic acid was removed by lyophilization and the residue was washed well with ethyl ether, yield 0.25 g. The compound absorbed at 5.75 μ (infrared) which is characteristic of formyl substitution; $\lambda_{max.}^{0.1\ N\ HCl}$ 345, 260 mμ; log ε 3.86, 4.15.

An attempted purification of this material by partition column chromatography[10] using a solvent system of heptane (8)–butanol (10)–2-methoxyethanol (6)–0.2 *M* phosphate buffer, pH 2.0 (10) yielded the hydrolyzed product, 6-demethyl-6-deoxy-7-hydroxytetracycline (VI).

6-Demethyl-6-deoxy-7-fluorotetracycline (VII).[8,9]—To a solution of 1.00 g. (1.57 mmoles) of 6-demethyl-6-deoxytetracycline-7-diazonium disulfate and 0.34 g. (3.14 mmoles) of sodium fluoroborate in 3.0 ml. water was added 250 ml. of glacial acetic acid. The solution was irradiated for 5 hr. at room temperature. The reaction mixture was lyophilized and the residue was distributed in a chloroform (4)–0.2 *M* phosphate buffer, pH 2.0 (2)–butanol (1) solution. The organic layer after evaporation to dryness was purified twice by partition column chromatography[10] using solvent systems of heptane (4)–butanol (5)–2-methoxyethanol (3)–0.2 *M* phosphate buffer, pH 2.0 (5) and heptane (60)–ethyl acetate (40)–methanol (15)–water (6); $[\alpha]^{25}D$ −83°; R_f 0.46; $\lambda_{max.}^{0.1\ N\ HCl}$ 345, 267 mμ; log ε 4.02, 4.23.

(8) Optical rotations were determined at a concentration of 0.1–0.5% in 0.1 *N* sulfuric acid.

(9) R_f values were determined in the system butanol, 0.2 *M* phosphate buffer, pH 2.

(10) The solid support for the stationary phase was diatomaceous earth (Johns-Manville Celite 547).

Anal. Calcd. for $C_{21}H_{21}N_2O_7F \cdot 2/3\ H_2O$: C, 57.0; H, 5.1; F, 4.3. Found: C, 57.1; H, 5.2; F, 3.9.

In addition to the 7-fluoro compound (VII), we obtained some IV and I.

On the Mechanism of the Arbuzov Rearrangement

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The Arbuzov rearrangement, $P(OR)_3 \xrightarrow{RX} RP(O)(OR)_2$, is generally considered to be a two-stage reaction with an ionic intermediate[2] shown as

$$R'X + :P(OR)_3 \longrightarrow [R'P(OR)_3]^+X^-$$

$$[R'P(OR)(O-R)]^+X^- \longrightarrow R'P(O)(OR) + RX$$

If the R groups in the two starting materials are the same, then a catalytic amount of the halide is sufficient to bring about isomerization of the phosphite. If they differ, the R group of the halide ends up bound directly to phosphorus, although as the reaction proceeds two different halides are present to compete for the phosphite.

With certain aromatic phosphites it has been possible to isolate the phosphonium intermediate, but no such direct confirmation of the course of the reaction has been obtained for aliphatic derivatives. It seemed to us that a study of the conductivity of a phosphite–alkyl halide mixture would bear directly on the mechanism of the reaction, and so we have made a conductometric study of the kinetics of the reaction of tri-*n*-butyl phosphite with ethyl iodide in acetonitrile at 31°.

Experimental

Materials.—Acetonitrile (Eastman Kodak Co.) was refluxed over barium oxide for several hours and distilled from barium oxide through a Vigreux column in a system protected by a calcium hydride tube. A middle fraction was collected, b.p. 76–78° uncor. (700 mm.). The specific

(1) (a) The Rev. F. C. Buck, S.J., Boston College High School, Boston, Massachusetts. The support of this work by a N. S. F. High School Teachers Research Participation Summer Institute at the University of Arizona is gratefully acknowledged; (b) To whom inquiries should be addressed.

(2) A. E. Arbuzov and L. V. Nesterov, *Dokl. Akad. Nauk SSSR*, **92**, 57 (1953); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 361 (1954); V. S. Abramov and G. A. Karp, *J. Gen. Chem. USSR*, 1823 (1954); "Soviet Research on Organo-Phosphorus Compounds 1949–1956," Consultants Bureau Inc., New York, pp. 17, 589; A. N. Pudovik, *Dokl. Akad. Nauk SSSR*, **84**, 519 (1952); *Chem. Abstr.*, **47**, 3226 (1953); G. M. Kosolapoff, *J. Am. Chem. Soc.*, **66**, 109 (1944); W. Gerrard and W. J. Green, *J. Chem. Soc.*, 2550 (1951); H. I. Jacobsen, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955).