# On the Total Synthesis of Tetracycline

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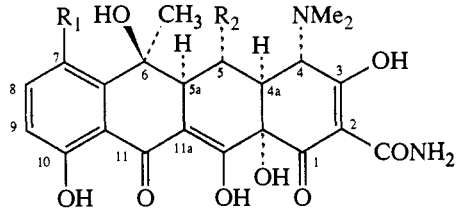
In spite of the success of a wide variety of synthetic approaches to the family of antibiotics[1] represented by the parent tetracycline (**1a**), the synthesis of 5-hydroxytetracycline[2] (**1b**) (terramycin)



1a, $R_1 = R_2 = H$ Tetracycline (TC)

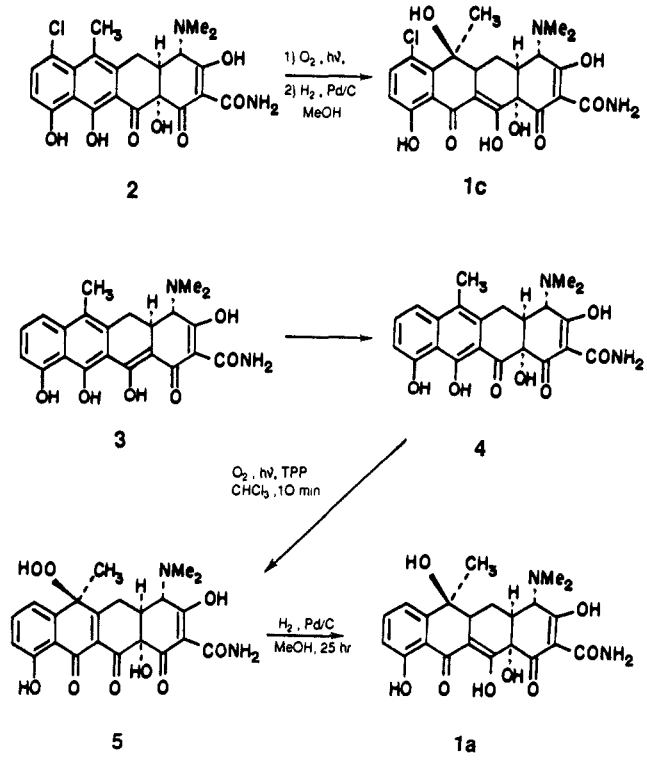
1b, $R_1 = H$; $R_2 = OH$ Terramycin

1c, $R_1 = Cl$; $R_2 = H$ Aureomycin

constitutes the sole complete de novo route to a naturally occurring member of this important class of antibiotic. Thus, a formal synthesis of aureomycin (7-chlorotetracycline, **1c**) depends on the conversion of the synthetic relay (±)-7-chloroanhydrotetracycline (**2**) to **1c** via a two-step "hydration" at the 5a,6-position, achieved stereospecifically in good yield by the photooxygenation/reduction route[3a,b] on optically active **2**, in turn obtained by dehydration of aureomycin. However, the photooxygenation reaction **4** → **5** was found to proceed poorly,[3a-d] if at all, on the parent anhydrotetracycline (ATC) (**4**), although evidence of both 6-hydroperoxidation and subsequent reduction to tetracycline (TC) (**1a**) has been reported.[3c]

In view of the availability of only qualitative evidence for conversion of **4** to **1a**, subsequent synthetic routes to tetracycline (**1a**) have avoided the anhydro route, and the recent total synthesis of (±)-12a-deoxyanhydrotetracycline (**3**) by Stork,[3d] although providing a formal link to **4** by 12a-hydroxylation,[4a] could not be claimed as a completed route to tetracycline in the absence of a reliable protocol for the introduction of the functionality and stereochemistry at positions 5a and 6. A solution to this problem would restore anhydrotetracycline (**4**) to the status of a viable synthetic relay to tetracycline (**1a**).

In the course of our studies on the dye-sensitized photooxygenation of enols and phenols,[5] we have reinvestigated the reaction of anhydrotetracycline (**4**) with singlet oxygen and now




report the successful conversion of this substrate to tetracycline (**1a**) in good yield via 6-β-hydroperoxidation.

Anydrotetracycline (**4**)[6] was photooxidized in water-cooled $CHCl_3$ with *meso*-tetraphenylporphine as sensitizer. Precipitation of the dye by addition of methanol, filtration, and removal of the solvent yielded 6-deoxy-6-hydroperoxy-5a,11a-dehydrotetracycline (**5**) (97%) as a pale yellow solid,[7] $[\alpha]^{25}_D$ 50.0° (*c* 0.4, MeOH), UV $CHCl_3$ ($1 \times 10^{-4}$ M) $\lambda_{max}$ (ε) 220 (36 000), 265 (43 000), 345 nm (6800).

Comparison of the $^1H$ NMR data showed a close correspondence of the chemical shifts for **5** (1.534 ($C_6$ $CH_3$), 7.228 ($C_7$ H)) and tetracycline (**1a**) whereas the chemical shifts for the 6-methyl group and the C-7 proton are quite different from the corresponding resonances in anhydrotetracycline (**4**) (2.409 ($C_6$ $CH_3$), 7.439 ($C_7$ H)). The strong IR absorption at 1700 $cm^{-1}$ and the absence of any olefinic proton between δ 4.0 and 6.5 in **5** provide evidence for the location of the double bond in the 5a,11a-position. Without further purification, the hydroperoxide **5** was catalytically hydrogenated (MeOH/Pd–C) to yield, after polyamide chromatography, tetracycline[8] (**1a**) (49%), identical in every respect[9] with the natural product.

With the demonstration of the practicality of this two-step sequence, the synthesis of (±)-12a-deoxyanhydrotetracycline[3d] (**3**) along with the previously reported[4] 12a-hydroxylation of (−)-**3** to anhydrotetracycline (**4**) constitutes for the first time a satis-

(1) Reviews: (a) Ito, I. *Nagoya-shiritsu Daigaku Yakugakubu Kenkyu Nenpo* **1975**, *23*, 1–88. (b) Kametani, T.; Fukumoto, K. *Kagaku Kogyo* **1979**, *30*, 1023–1031. (c) Durckheimer, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 721–734. (d) Blackwood, R. K. *Kirk and Othmer's Encyclopedia of Chemical Technology*, 2nd ed.; Wiley-Interscience: New York, 1969; Vol. 20, pp 1–33. (e) Money, T.; Scott, A. I. *Prog. Org. Chem.* **1968**, *22*, 435–456. (f) Clive, D. L. J. *Q. Rev. Chem. Soc.* **1968**, *22*, 4345–4356. (g) Conover, L. H. *Spec. Publ.—Chem. Soc.* **1956**, *No. 5*, 52–62. (h) Johnson, F. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley-Interscience: New York, 1973; Vol. I, p 331 ff.

(2) Muxfeldt, H.; Hardtmann, G.; Kathawala, F.; Vedejs, E.; Mooberry, J. G. *J. Am. Chem. Soc.* **1968**, *90*, 6534.

(3) (a) Scott, A. I.; Bedford, C. T. *J. Am. Chem. Soc.* **1962**, *84*, 2271. (b) Bedford, C. T. Ph.D. Thesis, University of Glasgow, 1963, p 106. (c) Schach von Wittenau, M. *J. Org. Chem.* **1964**, *29*, 2746. (d) Stork, G.; Hagedorn, A. A., III *J. Am. Chem. Soc.* **1978**, *100*, 3609.

(4) (a) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N. *Khim. Prir. Soedin.* **1966**, 141; (b) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V.; Popravko, S. A. Shemayakin, M. M. *Tetrahedron Lett.* **1967**, 131.

(5) Wasserman, H. H.; Pickett, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 4695.

(6) Samples of anhydrotetracycline hydrochloride (ATC-HCl) were kindly provided by Dr. M. K. Kunstmann (American Cyanamid) and Dr. M. Schach von Wittenau (Chas. Pfizer and Co.).

(7) A solution of ATC (**4**) (100 mg, 0.235 mmol) and meso-tetraphenylporphine (5 mg) in $CHCl_3$ (20 mL) was irradiated with a 650-W halogen–tungsten lamp while oxygen was bubbled through a closed system at cooling water temperature for 10 min. A TLC (C18 reversed phase, BuOH/HOAc/$H_2O$, 1/1/8) showed that all the ATC was oxidized.

(8) The crude 6-deoxy-6-hydroperoxy-5a(11a)-dehydrotetracycline (40 mg, 0.087 mmol) and 40 mg of 10% Pd on carbon in MeOH (15 mL) were subjected to hydrogenation (48 psi) for 2.5 h at room temperature. A TLC (C18 reversed phase, $CH_3CH$/HOAc/$H_2O$, 8/1/11) showed that there was a spot identical in Rf to TC which was UV (365 nm) active. Purification on a polyamide column gave 19 mg (49%) of the pure TC as a pale yellow solid: mp 175–180 °C dec; $[\alpha]^{25}_D$ −244.67 (*c* 1.05, MeOH);[9] UV (0.01 M HCl in MeOH) $\lambda_{max}$ (ε) 268 (40 000), 363 mn (28 000).

(9) (a) The Merck Index, 10th ed.: tetracycline trihydrate, mp 170–175 °C dec (swells at 165 °C); $[\alpha]^{25}_D$ −257.9° (*c* 1, 0.1 N HCl); $[\alpha]^{25}_D$ − 239° (*c* 1, MeOH). Absorption maxima in 0.1 N HCl at 220 (ε 13 000), 268 (ε 18 040), 355 nm (ε 13 320). (b) A sample of tetracycline (purchased from Sigma) recrystallized from methanol: $[\alpha]^{25}_D$ −233.23° (*c* 1.06, MeOH).

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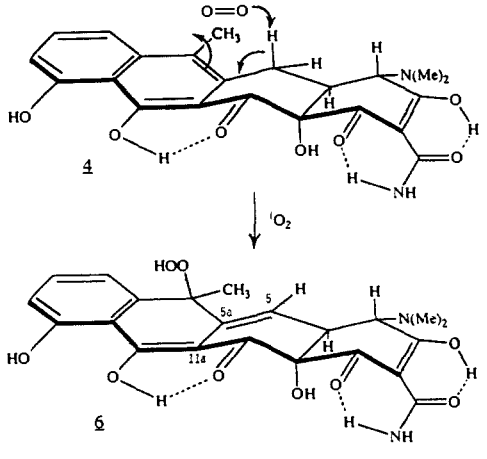
factory route to the parent antibiotic, requiring only the optical resolution of (±)-**3** to complete the total synthesis of tetracycline. In addition, the successful outcome of the dye-sensitized oxidation allows the preparation of 5a,11a-dehydrotetracycline (**5**; OOH = OH), a promulgated (but hitherto untested) intermediate in the biosynthesis of tetracycline.[1e]

The remarkable stereospecificity in the introduction of the hydroperoxide from the β-face at C-6 may be attributed to the operation of an ene reaction involving the 5β-proton yielding the kinetic intermediate **6**, a 5a,5-double bond isomer of **5**, followed by equilibration of the double bond in **6** to the 5a,11a-position in **5**.



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**Supplementary Material Available:** $^1$H NMR, infrared, and UV data, physical constants, rotations, and purification procedures for **4**, **5**, and **1a** (4 pages). Ordering information is given on any current masthead page.

## On Visible Transients in Gas Phase UV Photolysis of Transition Metal Compounds: Experimental and Theoretical Results for $Ni(CO)_4$

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In this paper we present and discuss the luminiscence spectrum resulting from photolysis of $Ni(CO)_4$ with a XeCl laser (308 nm). To our knowledge this is the first observation of an emission from a metal carbonyl compound. Based on LCGTO-Xα calculations we propose the following three-step mechanism (excitation, dissociation, fragment luminiscence) involving a transition-metal carbonyl fragment:

$$Ni(CO)_4 + h\nu \rightarrow Ni(CO)_4^* \rightarrow Ni(CO)_3^* + CO \rightarrow Ni(CO)_3 + h\tilde{\nu} \quad (1)$$

Our calculations indicate that the excited states of both $Ni(CO)_4$ and of $Ni(CO)_3$ show pronounced metal-to-CO charge-transfer character.[1]

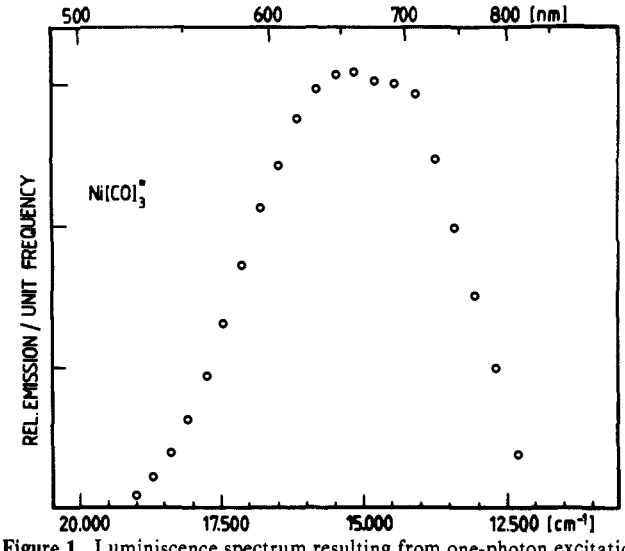


**Figure 1.** Luminiscence spectrum resulting from one-photon excitation of $Ni(CO)_4$ with a XeCl laser (λ = 308 nm, $\sigma = 2.4 \times 10^{-18}$ cm$^2$). According to our analysis this emission can be assigned to a CT transition of an electronically excited $Ni(CO)_3^*$ photofragment.

Our study is prompted by the rapidly increasing interest in photolytic reactions of homoleptic complexes resulting from their central role in photocatalysis[2] and laser-induced metal vapor deposition.[3] It is well-known that these compounds readily decompose upon pulsed UV laser excitation. However, until now, only the bare metal atom[4] or the CO ligands[5] could be detected in the vapor phase. Consequently, detailed information on the linking reaction channels are quite scarce; a notable exception is the recent work on $Cr(CO)_6$.[6] Furthermore, electronically excited fragments may act as energy reservoirs in the course of a multistep laser-induced decomposition process.[7]

To our knowledge, in the case of transition-metal carbonyls no direct evidence for such excited transients has been reported previously. This is somewhat surprising because we find that the fragment emission is strong enough to make the structure of a pulsed $Ni(CO)_4$ molecular beam visible with the naked eye after excitation with a KrF or XeCl laser. The emission spectrum obtained after excitation with a XeCl laser (4.0 eV) is shown in Figure 1. It has been corrected for the spectral sensitivity of the spectrometer. Experimental details have been discussed elsewhere.[8]

The spectrum is surprisingly broad and seems to be continuous. From our experience with related compounds,[8] no further structure is to be expected when the resolution is enhanced. The emission intensity maximum occurs at 650 nm (1.90 eV), giving the beam a reddish appearance. The luminiscence lifetime is >10 μs, therefore the spectrum was recorded during the first 5 μs using a gated optical spectrum analyzer at a pressure of 6 μbar to exclude perturbing collision processes. The one-photon nature of the absorption process leading to luminiscence was established by continuously reducing the laser intensity. We preliminarily

(1) Jörg, H.; Kotzian, M.; Rösch, N., to be submitted for publication.
(2) Whetten, R. L.; Fu, K.-J.; Grant, E. R. *J. Chem. Phys.* **1982**, *77*, 3769-3770.
(3) Schröder, H.; Kompa, K. L.; Masci, D.; Gianinoni, I. *Appl. Phys. A* **1985**, *38*, 227-233 and references cited therein.
(4) (a) Duncan, M. A.; Dietz, T. G.; Smalley, R. E. *Chem. Phys.* **1979**, *44*, 415-419. (b) Fisanick, G. J.; Gedanken, A.; Eichelberger, T. S.; Kuebler, N. A.; Robin, M. B. *J. Chem. Phys.* **1981**, *75*, 5215-5225. (c) Mitchell, S. A.; Hackett, P. A. *J. Chem. Phys.* **1983**, *79*, 4815-4822.
(5) Whetten, R. L.; Fu, K.-J.; Grant, E. R. *J. Chem. Phys.* **1983**, *79*, 4899-4911.
(6) Fletcher, T. R.; Rosenfeld, R. N. *J. Am. Chem. Soc.* **1985**, *107*, 2203-2212.
(7) Nathanson, G.; Gitlin, B.; Rosan, A. M.; Yardley, J. T. *J. Chem. Phys.* **1981**, *74*, 361-369. Yardley, J. T.; Gitlin, B.; Nathanson, G.; Rosan, A. M. *J. Chem. Phys.* **1981**, *74*, 370-378.
(8) Kompa, K. L.; Lamprecht, H.; Schröder, H.; Puretzky, A. A.; Tyakht, V. V. *J. Chem. Phys.* **1986**, *84*, 2020.

0002-7863/86/1508-4238$01.50/0 