coagulated. The supernatant liquid was decanted and treated with a further 1 g of silver oxide with stirring overnight. The mixture was filtered, and the combined silver salt residues were washed throughly with water at 50 °C. The combined aqueous fractions were evaporated to ca. 5 mL while the temperature was kept below 35 °C. A brown solution was obtained which was acidified with concentrated hydriodic acid. A brown precipitate (0.25 g) formed that on recrystallization from methanol gave 0.15 g (22%) of **2** (I^-), mp >300 °C; field-desorption mass spectrum, $m/z = 208$. Anal. Calcd for $C_{14}H_{26}NI$: C, 50.15; H, 7.82; N, 4.18. Found: C, 49.61; H, 7.75; N, 3.89.

A slurry of 20 mg of (I^-) in 1 mL of D_2O was treated with excess silver oxide at ambient temperature for 3 h. Filtration gave a D_2O solution of **2**(OH^-), which was used for the NMR measurements: ^1H NMR (D_2O) see Figure 1 and Table I; ^{13}C NMR (D_2O) δ 67.9, 59.0, 50.9, 48.9, 29.9, 29.7, 29.2, 27.7, 19.2, 19.1, 17.9, 17.6, 17.0, 14.0.

Acknowledgment. The financial assistance of the Natural Sciences and Engineering Research Council of Canada made this work possible. The 100-MHz ^{13}C and 400-MHz ^1H NMR spectra were run at the Southwestern Ontario NMR Center funded by a Major Installation Grant from NSERC.

Registry No. 2 I^-, 82510-95-0; **2** OH^-, 82521-43-5; **3**, 82510-96-1; **4** Br^-, 82510-97-2; 5-chloro-1-pentene, 928-50-7; 9a-cyanoquinolizidine, 23805-76-7; 4-penten-1-ol, 821-09-0.

11a-Chlorination of the Shemyakin Tricyclic Ketone

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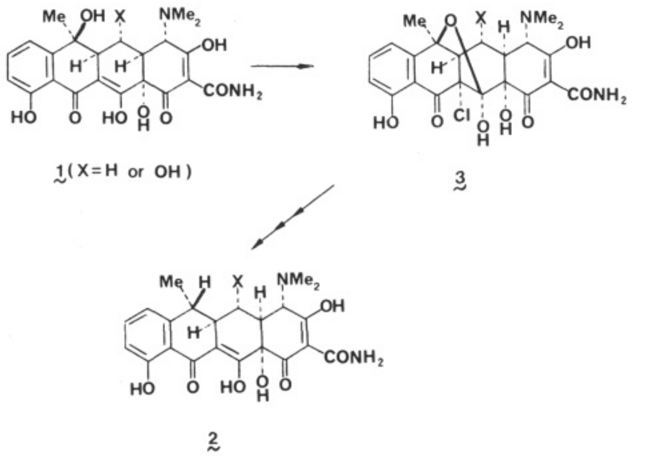
Received February 2, 1982

The extreme complexity of the tetracycline antibiotics has meant that very few useful chemical modifications of these antibiotics have been accomplished.[1] A notable exception is the valuable sequence of reactions that convert tetracycline **1** into 6α-deoxytetracycline **2** through the intermediacy of 11a-chlorotetracycline 6,12-hemiketal **3**.[2]



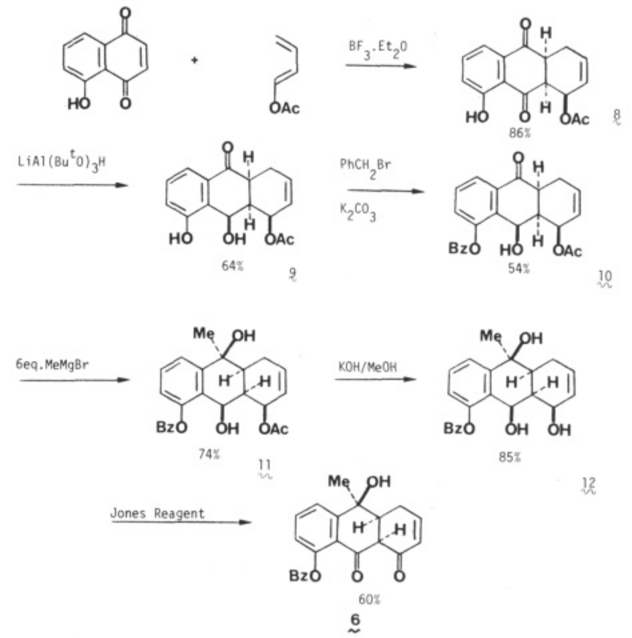
1 (X = H or OH)

3

2

Compared to tetracycline itself, the 11a-chloro 6,12-hemiketal **3** is more stable to both acids and bases. It can be easily converted back into tetracycline by mild reduction with zinc in dilute hydrochloric acid or aqueous sodium hydrosulfite. Consequently the 11a-chlorine atom can be viewed both as a stabilizing substituent and a block to oxidation at position 11a. Both these properties could be valuable in any projected synthesis of a tetracycline where the 12a-hydroxyl group has to be selectively introduced without oxidation at the 11a-position.

Scheme I



[a] Details are given in the supplementary material.

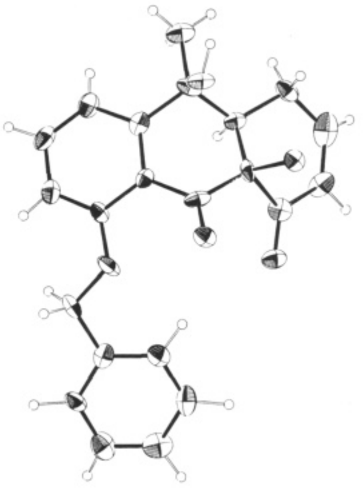


Figure 1. Structure of **7**.

The 11a-chlorination of tetracycline **1** (X = H) or terramycin (**1**, X = OH) is usually carried out with *N*-chlorosuccinimide, and the only product isolated is **3**, where the chlorine is α, and the 6-hydroxyl group has formed a hemiacetal with the 12-ketone. We were intrigued by the idea of making a tricyclic analogue of **3**, namely, **4**, from the so-called Shemyakin ketone **5**. The Shemyakin ketone **5** was made by using the same sequence as originally described,[3] although with substantial exper-

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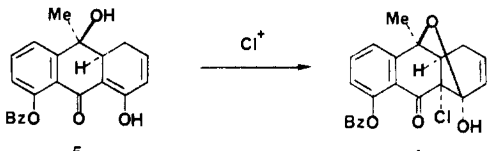
*To whom correspondence should be addressed at Indiana University.

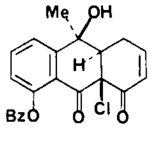
(1) Clive, D. L. J. *Q. Rev., Chem. Soc.* **1968**, *22*, 435. Blackwood, R. K. "Kirk-Othmer Encyclopedia of Chemical Technology", 2nd ed.,; Wiley: New York, 1969; Vol. 20, p 1.

(2) Blackwood, R. K.; Beereboom, J. J.; Rennard, H. H.; Schach von Wittenau, M.; Stephens, C. R. *J. Am. Chem. Soc.* **1963**, *85*, 3943.



5 4

imental modifications that considerably improved the yields and purification methods. A brief outline of this synthesis is shown in Scheme I. When the diketone **6** is chromatographed over silica gel, it is converted into the Shemyakin ketone **5**, although we found **6** to be entirely equivalent to **5** in its response to chlorinating agents. Treatment of **6** with *N*-chlorosuccinimide in dimethoxyethane at 20 °C gave a single crystalline monochloro derivative, **7**. Its structure was not readily apparent from spectral data; consequently, a single-crystal X-ray analysis was conducted[4] and the results are shown in Figure 1. Other chlorination reagents such as *tert*-butyl hypochlorite and chloramine T gave similar results although not so cleanly.



7

The exclusive formation of the *trans*-11a-chloro adduct **7** strongly suggests that for the tetracyclines **1** (X = H or OH) an intramolecular association of the electrophilic chlorinating agent and the 12a-hydroxyl group takes place, thereby directing the chlorine atom into the 11a-position from the same side (α) as the 12a-hydroxyl group. The 5-hydroxyl group cannot be responsible for this effect since tetracycline itself **1** (X = H) gives the 11aα-chloro compound **3** (X = H). It appears likely that in the case of **6** the chlorine atom enters the more hindered concave side by prior hydrogen bonding to the 6-hydroxyl group.

Experimental Section

4,10-Dioxo-4aβ-chloro-5-(benzyloxy)-9β-hydroxy-9α-methyl-1,4,9,9aα,10-pentahydroanthracene (7). The dienolone **6** (100 mg, 0.287 mmol) in dimethoxyethane (3 mL) was treated with *N*-chlorosuccinimide (28 mg, 0.287 mmol) at 20 °C. After 1 h the solvent was removed in vacuo and the residue added to ethanol (0.25 mL) and water (15 mL). The aqueous solution was extracted with chloroform (3 × 10 mL), and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in hot dichloromethane and cooled to 4 °C to give crystals of **7**: 84 mg (77%); mp 124–126 °C dec; IR ($CHCl_3$) ν_{max} 3570, 1720, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (3 H, s), 2.60–3.20 (3 H, m), 5.16 (2 H, s), 6.14 (1 H, d, J = 7.5 Hz), 6.80–7.56 (9 H, m); ^{13}C NMR (20.1 MHz, $CDCl_3$) 188.3, 186.2, 157.7, 149.2, 148.0, 136.5, 134.6, 128.7, 127.8, 126.9, 119.3, 113.5, 70.8, 70.6, 65.7, 48.9, 30.0, 22.3. Anal. Calcd for $C_{22}H_{19}O_4Cl$: C, 69.02; H, 5.00; Cl, 9.26. Found: C, 69.27; H, 5.06; Cl, 8.99.

Registry No. 5, 67122-45-6; **6**, 82494-99-3; **7**, 82495-00-9; **8**, 73794-49-7; **9**, 73794-50-0; **10**, 82495-01-0; **11**, 82495-02-1; **12**, 82495-03-2; 5-hydroxy-1,4-naphthalenedione, 481-39-0; 1,3-butadien-1-ol acetate, 1515-76-0.

Supplementary Material Available: Experimental procedures and data for compounds **6** and **8–12**, line drawings of the molecules, and fractional coordinates, anisotropic thermal parameters, and bond distances and angles for compound **7** (8 pages). Ordering information is given on any current masthead page.

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(3) Inhoffen, H. H.; Muxfeldt, H.; Schaefer, H.; Kramer, H. *Croat. Chem. Acta.* **1957**, *29*, 329. Kolosov, M. N.; Popravko, S. A.; Gurevich, A. I.; Korobko, V. G.; Vasina, I. V.; Shemyakin, M. M. *Zh. Obshch. Khim.* **1964**, *34*, 2534. Kolosov, M. N.; Popravko, S. A.; Korobko, V. G.; Shemyakin, M. M. *Ibid.* **1964**, *34*, 2540. Kolosov, M. N.; Popravko, S. A.; Korobko, V. G.; Karapetyan, M. G.; Shemyakin, M. M. *Ibid.* **1964**, *34*, 2547. Kolosov, M. N.; Popravko, S. A.; Shemyakin, M. M. *Justus Liebigs Ann. Chem.* **1963**, *86*, 668. For a recent modification see: Stork, G.; Hagedorn A. A., III *J. Am. Chem. Soc.* **1978**, *100*, 3609. These authors show that the $BF_3 \cdot Et_2O$-catalyzed cyclization of juglone with 1-acetoxybutadiene gives almost exclusively the single regioisomer shown in Scheme I.

(4) A single crystal of **7** of dimensions 0.25 × 0.35 × 0.35 mm was cooled to −165 °C on a computer-automated Picker goniostat. Complete details of the low-temperature device, goniostat, and contorl system are given in: *Inorg. Chem.*, **1980**, *19*, 2755. Crystal data are as follows: space group $P2_1/c$, a = 11.124 (13) Å, b = 11.105 (14) Å, c = 14.438 (19) Å, β = 95.21 (5) Å, and d_{calcd} = 1.432 g cm^{-3} d_{calcd} for Z = 4. Data was collected for $+h$, $+k$ ±l in the range $5 \leq 2\theta < 50°$ by using graphite monochromated Mo Kα radiation (λ = 0.71069 Å). A scan speed of 4° min^{-1} over a range of 2° in 2θ with a 5-s stationary background were used for the $\pm 2\theta$ continuous scan. The structure was solved by direct methods, and the 1491 data with $F > 3\sigma(F)$ (out of 2318 unique data) were used in the refinement. All hydrogen atoms were located and refined isotropically, with anisotropic thermal parameters for the nonhydrogen atoms. Final residual are R(F) = 0.083 and R(wF) = 0.068. Fractional coordinates, thermal parameters, bonded distances, and bonded angles are available as supplementary data. Complete crystallographic details are also available from the Chemistry Library, Indiana University, Bloomington, IN 47405. Request IUMSC Report 8043.

Organoiron Complexes in Organic Synthesis. 25.[1] Complete Stereocontrol in the Synthesis of 4,4,5-Trisubstituted Cyclohexenones

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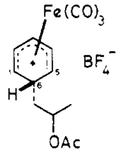
Received March 2, 1982

We recently described[2-4] approaches to the synthesis of 6-exo-substituted tricarbonylcyclohexadienyliumiron cationic complexes **1** and **2** using thallium (III) or $FeCl_3$/silica gel promoted cyclization of hydroxy-substituted compounds such as **3a** to give tetrahydrobenzofuran complexes of type **4**. Treatment of **4** with acid (HBF_4) in the presence of acetic anhydride caused opening of the tetrahydrofuran ring and concomitant acetylation of the hydroxy group to give the dienylium complexes. In our earlier work the latter complexes were produced having rather bulky 6-exo substituents, so that addition of nucleophiles to the dienylium ligand to give complexes of structure **3b** occurred either in very poor yield (ca. 40%) or not at all in cases with very bulky substituents, the nucleophile preferring instead to attack a carbonyl ligand or to cause decomplexation of the dienylium ligand (mechanism unknown). However, despite our early lack of success and in view of



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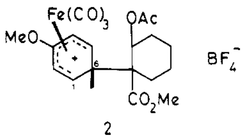

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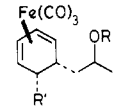
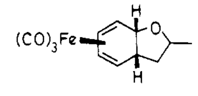


3a R = R' = H

3b R = Ac, R' = SPh, CH(CO$_2$Me)$_2$



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