# Reaction of Tetracycline Hydrochloride with *N*-Chlorosuccinimide: *X*-Ray Crystal Structure of the Major Product

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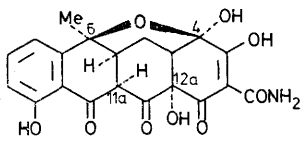
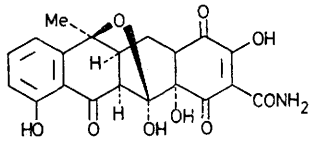
*Summary* The major product of the reaction of tetracycline hydrochloride with *N*-chlorosuccinimide has been shown by spectroscopic and *X*-ray analysis to be the novel bridged tetracycline derivative (**3**).

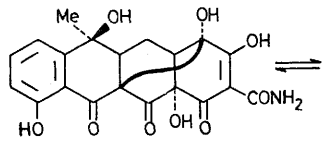
THE reaction of tetracycline hydrochloride with *N*-chlorosuccinimide is reported to give the tetracycloxide (**1**).[1] As similar derivatives have been converted into tetracyclines[1,2] this compound represents a potential synthetic target for our approach to tetracycline. Gurevich *et al.*[3] have reported that two products are formed in this reaction and have assigned the structure (**1**) to the minor component and (**2**) to the major product. We have repeated the reaction, although we disagree with the structural assignment (*vide infra*). The reaction proceeds smoothly to give two products; the major product can be obtained pure by crystallisation from methanol.



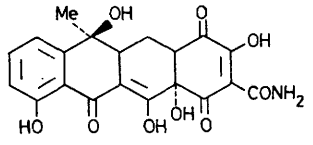
(1)



(2)



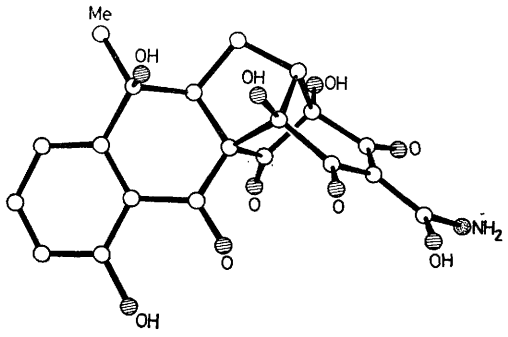
(3)



(4)

The spectroscopic data for the major compound (Table), though consistent with the previous reports are inconsistent with structure (**1**) or (**2**). For example, the i.r. band at 1770 $cm^{-1}$ is at high wavenumber and is more typical of either a $\gamma$-lactonic or a strained ring carbonyl group. Also Fourier transform $^1H$ n.m.r. spectroscopy failed to show the absorption that would be expected for 11a-H. The u.v. data indicate both a tetralone and a ring A chromophore similar to other tetracycloxides but clearly very different to the spectrum expected for the species (**2**). We conclude, therefore, that the true structure of the major product is in fact the novel 11a,4-bridged compound (**3**). This has been confirmed by *X*-ray crystallographic analysis of the dimethanolate.

*Crystal data:* monoclinic, space group $P2_1$, $a = 7{\cdot}579(1)$, $b = 13{\cdot}534(1)$, $c = 10{\cdot}744(1)$ Å, $\beta = 96{\cdot}907(5)°$, $Z = 2$. Intensities of 2215 reflections ($\theta \leqslant 71°$) were measured on a Siemens diffractometer using filtered Cu-$K_\alpha$ radiation. The structure, which has been solved by direct methods and refined to a current $R$ value of 0·062, is illustrated in the Figure. In the solid state the carbonyl group of the C-2 amide is substantially enolised.‡



FIGURE

TABLE

| Compound | M.p./°C | ν(C=O)/$cm^{-1}$ | $\lambda_{max}$ (0·01N HCl–MeOH)/nm | $[\alpha]_D$/° |
|---|---|---|---|---|
| (**1**)[a] | — | 1754[e] | 268 (25,100), 346 (5,250)[e] | — |
| (**2**)[b] | 188—192 | 1765 | 267 (18,600), 347 (4,370) | −84[f] |
| (**1**)[c] | 193—197 | 1723 | 258 (21,900), 337 (4,370) | −104[f] |
| (**3**)[d] | 181—183 (decomp.) | 1770 | 268 (26,500), 346 (4,820) | −82[g] |

[a] Obtained in ref. 1. [b] Major product obtained in ref. 3. [c] Minor product obtained in ref. 3. [d] Major product of this work. [e] As the potassium salt. [f] $c = 0{\cdot}1$, MeOH. [g] $c = 0{\cdot}5$, EtOH.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

The minor product, for which we were unable to obtain a pure sample, shows a doublet in the n.m.r. spectrum at $\delta$ 4·14 which is typical of 11a-H. On this basis and on the basis of other data, this product can be assigned the structure (**1**).

The major product (**3**), which contains the 11a,4-bridge, is related to the quinonoid compound (**4**) by a retro-aldol reaction. In keeping with this idea, compound (**3**) undergoes reactions typical of (**4**). Thus the 4-oxime and 4-hydrazone can be prepared in 94 and 89% yields, respectively.

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[1] R. K. Blackwood and C. R. Stephens, *Canad. J. Chem.*, 1965, **43**, 1382.
[2] R. C. Esse, J. A. Lowery, C. R. Tamorria, and G. M. Sieger, *J. Amer. Chem. Soc.*, 1964, **86**, 3875.
[3] A. I. Gurevich, M. G. Karapetyan, and M. N. Kolosov, *Chem. Natural Compounds*, 1970, **6**, 240.