

present derivatives are under further study in these laboratories.

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### Electron Spin Resonance Spectra of Different Solvates of *m*-Nitrophenol Negative Ion in a Mixed Solvent

Sir:

It is well known that e.s.r. spectra of many organic radicals and radical ions in solution are very sensitive to solvent composition.<sup>1</sup> Electron-nuclei spin-spin

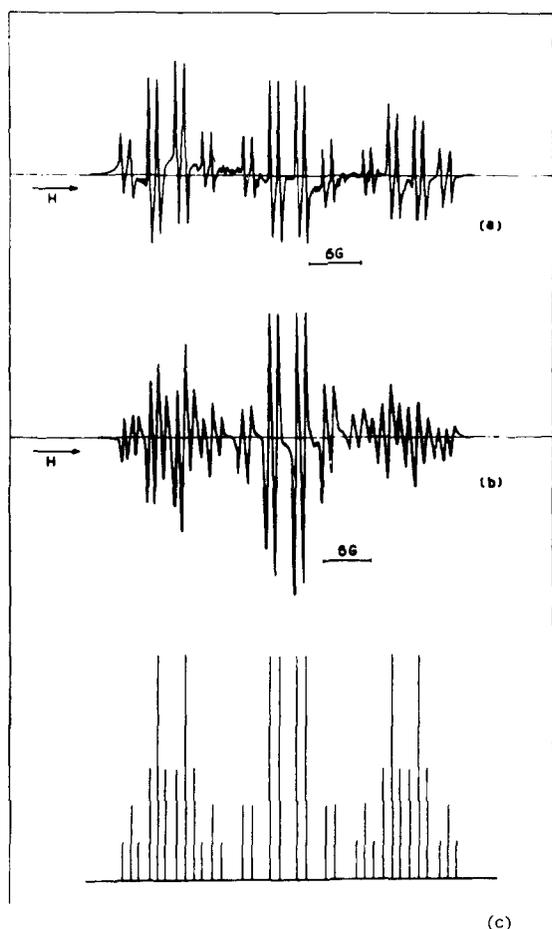


Fig. 1.—E.s.r. first derivative spectrum of *m*-nitrophenol ion in 50% water-DMF with electrolyte 0.1 *M*  $\text{NEt}_4\text{ClO}_4$ : a, at room temperature; b, same at 0°; c, reconstruction of spectrum b based on superposition of the two spectra arising from two species in 1:1 ratio and differing only in  $a_N$ .

coupling constants undergo conspicuous variations with solvent and the behavior has been explained<sup>2</sup> through the formation of "solvates" or "complexes" in which the radical is linked to one or more solvent molecules as for example in the model reaction



where R is the radical and  $\text{S}_1$  and  $\text{S}_2$  are the two solvents.

The e.s.r. spectra obtained up to now in these cases always presented hyperfine patterns indicating coupling

constants corresponding to weighted averages of the values existing in the pure solvents.

During the course of an investigation of the e.s.r. spectra of *m*-nitrophenol negative ion produced by electrolysis in water-dimethylformamide (DMF) mixtures we have obtained spectra which are very clearly due to the superposition of two radical species which we logically identify with two different solvates.

Figure 1a shows the spectrum of *m*-nitrophenol anion in an approximately 50% mixture of water and DMF. The hyperfine pattern is due to a major triplet arising from the nitrogen coupling of 14.6 gauss; this splits into quartets (intensity 1:3:3:1) due to three almost equivalent protons and furthermore into doublets, the last splitting arising from the remaining proton with the smallest coupling constant.

The pattern remains practically the same in going from pure water to pure DMF, the only feature influenced being the main nitrogen splitting which decreases smoothly from 14.6 gauss in pure water to 12.3 gauss in pure DMF. The proton coupling constants are not influenced much by solvent composition at least up to almost unit DMF mole fraction where differences are noted among the three almost equivalent protons.

Figure 1b shows the spectrum obtained from the same solution of Fig. 1a at a lower temperature. The pattern of the central group is not affected but the two side groups now have a larger number of lines. The reconstruction of Fig. 1c shows how the pattern is easily explained on the basis of the superposition of two spectra of the type of Fig. 1a differing only in the major nitrogen splitting. Some of the lines of the side groups have a greater width because the overlapping is not so perfect as postulated in the reconstruction. We note also that in both spectra the high field group lines are wider than the corresponding low field ones as is currently observed in many cases.<sup>3</sup>

It is clear from this experiment that, in the case of sufficiently large differences among some coupling constants of the two alleged "solvates"  $\text{RS}_1$  and  $\text{RS}_2$ , it is possible to obtain conditions of sufficiently low rate of exchange among the two species such that the two spectra can be detected at the same time. Further details on this phenomenon and a comprehensive quantitative discussion will be published shortly.

(3) P. B. Ayscough, F. P. Sargent, and R. Wilson, *J. Chem. Soc.*, 5418 (1963).

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### Novel C-4 Modified Tetracycline Derivatives

Sir:

The reaction of amphoteric tetracycline 1 with N-chlorosuccinimide to yield 11a-chlorotetracycline-6,12-hemiketal 2 has been reported.<sup>1</sup> A less than drastic change in chlorination conditions—treatment of tetracycline hydrochloride with N-chlorosuccinimide in water—leads to the isolation of a drastically different product, 4-oxo-4-dedimethylaminotetracycline 4,6-hem-

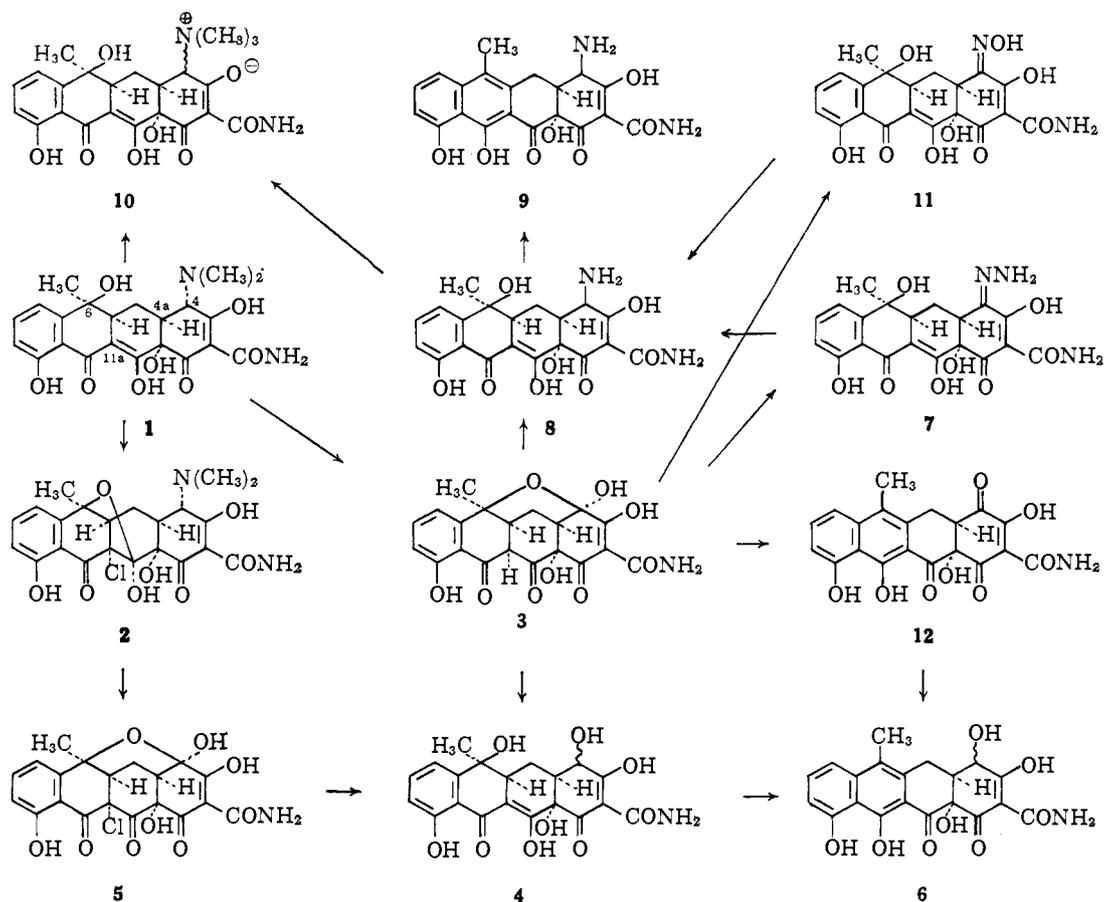
(1) R. K. Blackwood, J. J. Beereboom, H. H. Rennard, M. Schach von Wittenau, and C. R. Stephens, *J. Am. Chem. Soc.*, **83**, 2778 (1961); **85**, 3943 (1963).

(1) E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **36**, 1944 (1962).

(2) J. Gendell, J. H. Freed, and G. K. Fraenkel, *ibid.*, **37**, 2832 (1962).

hemiketal **3**.<sup>2</sup> *Anal.* Found for  $C_{20}H_{16}O_9NK \cdot 0.5H_2O$ : C, 52.0; H, 3.8; N, 3.2; Cl, 0.0; K, 8.2;  $H_2O$ , 1.7. Absorption peaks occur at  $\lambda_{max}^{MeOH-0.01 N HCl}$  268 and 346  $m\mu$  ( $\log \epsilon$  4.40 and 3.72);  $\lambda_{max}^{MeOH-0.01 N NaOH}$  very unstable, includes  $\lambda_{max} \sim 370 m\mu$  ( $\log \epsilon \sim 4.4$ );  $\lambda_{max}^{KBr}$  5.7  $\mu$ . The hemiketal **3** is readily reduced to alcohol **4**, by catalytic hydrogenation, sodium hydrosulfite, or zinc dust;  $\lambda_{max}^{MeOH-0.01 N HCl}$  257 and 362  $m\mu$  ( $\log \epsilon$  4.23 and 4.20). *Anal.* Found for  $C_{20}H_{19}NO_9$ : C, 57.3; H, 4.6; N, 3.2. An alternative preparation of the alcohol is *via* catalytic hydrogenation of **5**;  $\lambda_{max}^{MeOH-0.01 N HCl}$  258 and 343  $m\mu$  ( $\log \epsilon$  4.42 and 3.68);  $\lambda_{max}^{KBr}$  5.77  $\mu$ . *Anal.* Found for  $C_{20}H_{16}O_9NCl$ : C, 53.0; H, 3.7; N, 2.8; Cl, 8.0. Compound **5** is formed by analogous N-chlorosuccinimide treatment of **2**.

$O_3N_3 \cdot H_2O$ : C, 53.8; H, 4.6; N, 9.0. Reduction of **7** with zinc dust in aqueous acetic acid or with sodium hydrosulfite yields 4-epi-4-amino-4-dedimethylaminotetracycline (**8**),  $\lambda_{max}^{MeOH-0.01 N HCl}$  260 and 360  $m\mu$  ( $\log \epsilon$  4.25 and 4.17). *Anal.* Found for  $C_{20}H_{20}O_8N_2 \cdot 1.5(CH_3)_2NCHO$ : C, 55.8; H, 5.9; N, 9.2. The 5a,6-anhydro derivative **9** gave  $\lambda_{max}^{MeOH-0.01 N HCl}$  223, 272, and 423  $m\mu$  ( $\log \epsilon$  4.45, 4.71, and 3.93). *Anal.* Found for  $C_{20}H_{18}O_7N_2 \cdot HCl \cdot (CH_2)_4O$ : C, 56.7; H, 5.1; N, 5.5;  $Cl^-$ , 7.1;  $NH_2$ , 3.2. Stereochemistry at C-4a is assigned on the basis of smooth conversion in acetone, propylene oxide, and methyl iodide to tetracycline methyl betaine **10**.<sup>4,5</sup> Stereochemistry at C-4 is tentatively assigned on the basis of the short wave length ultraviolet maximum and by virtue of the presence of a minor, *much more antibacterial* substance



Acid degradation of the alcohol **4** yields the corresponding 5a,6-anhydro derivative **6**,  $\lambda_{max}^{MeOH-0.01 N HCl}$  222, 262, 310, and 423  $m\mu$  ( $\log \epsilon$  4.46, 4.70, 3.68, and 4.01). *Anal.* Found for  $C_{20}H_{17}O_8N$ : C, 59.8; H, 4.5; N, 3.3. The anhydro alcohol **6** may also be obtained by the sequence **3**  $\rightarrow$  **12**  $\rightarrow$  **6** (anhydrous hydrogen fluoride followed by sodium hydrosulfite reduction).

The 4,6-hemiketal **3** undergoes a variety of other reactions. For example, reaction with hydrazine yields the hydrazone **7**,  $\lambda_{max}^{MeOH-0.01 N HCl}$  264 and 335  $m\mu$  ( $\log \epsilon$  4.16 and 4.53);  $\lambda_{max}^{MeOH-0.01 N NaOH}$  261, 323, and 373  $m\mu$  ( $\log \epsilon$  4.33, 4.25, and 4.29). *Anal.* Found for  $C_{20}H_{19}$ -

in preparations of the amine **8**, which paper chromatographic studies indicate to be epimeric in nature. The 4-amino compound **8** may also be obtained by zinc reduction of the oxime **11** or by direct reductive amination of 4-oxotetracycline **3** ( $H_2$ ,  $PtO_2$ ,  $MgCl_2$ , and excess  $NH_4OH$  in dimethylformamide solution).

Extension of the reactions described herein to other tetracyclines, to substituted hydrazines, and to other amines is in progress.

(4) Under these conditions tetracycline and 4-epitetracycline yield the same product.

(5) J. H. Boothe, G. E. Bonvicino, C. W. Waller, J. P. Petisi, R. W. Wilkinson, and R. B. Broschard, *J. Am. Chem. Soc.*, **80**, 1654 (1958).

(2) For leading references concerning the conversion of tertiary amines to aldehydes with N-bromosuccinimide and with hypochlorous acid see R. Fuller, *Chem. Rev.*, **63**, 21 (1963), and A. J. Ellis and F. G. Soper, *J. Chem. Soc.*, 1750 (1954), respectively.

(3) The 4,6-hemiketal structure for **5** is presumed on the basis of analogy to **3**.

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