process[7]. Dehydration of XVIII and introduction of the 9α-fluoro group by established methods[8] yielded 9α,16α-difluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione XX, m.p. 265–268°.

Preliminary anti-inflammatory assays[9] showed 16α-fluoroprednisolone acetate XVIII to be about 16 times as active as hydrocortisone and the 9α-fluoro-derivative XX to be about 75 times as active as hydrocortisone[10].

(7) D. E. Ayer and W. P. Schneider, THIS JOURNAL, **82**, 1249 (1960).
(8) J. Fried and E. Sabo, *ibid.*, **76**, 1455 (1954).
(9) A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957).
(10) The authors are indebted to W. E. Dulin, S. C. Lyster and associates for the biological data, to J. L. Johnson and W. A. Struck and associates for elemental and spectral analyses and rotations, to G. Slomp for n.m.r. data and G. E. VandenBerg for technical assistance.

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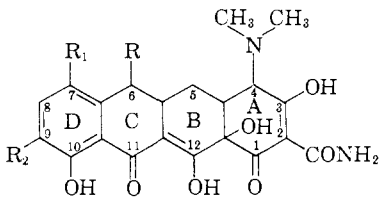
6-DEOXYTETRACYCLINES. I. CHEMICAL MODIFICATION BY ELECTROPHILIC SUBSTITUTION

Sir:

The chemical stability of the recently reported[1,2] broad spectrum antibiotics, 6-deoxytetracycline (I) and 6-demethyl-6-deoxytetracyline (II), has permitted the study of a series of electrophilic substitution reactions under strongly acidic conditions. From two such reactions, nitration and bromination, we have obtained several new derivatives which possess antibacterial properties. These properties are being evaluated and will be the subject of a future communication.



I, R = CH_3, R_1 = R_2 = H
II, R = R_1 = R_2 = H
III, R = R_2 = H, R_1 = Br
IV, R = R_2 = H, R_1 = I
V, R = CH_3, R_1 = Br, R_2 = H
VI, R = CH_3, R_1 = I, R_2 = H
VII, R = R_2 = H, R_1 = NO_2
VIII, R = R_1 = H, R_2 = NO_2
IX, R = CH_3, R_1 = NO_2, R_2 = H
X, R = CH_3, R_1 = H, R_2 = NO_2
XI, R = R_2 = H, R_1 = NH_2
XII, R = R_1 = H, R_2 = NH_2
XIII, R = CH_3, R_1 = H, R_2 = NH_2
XIV, R = CH_3, R_1 = Br, R_2 = NH_2
XV, R = CH_3, R_1 = NO_2, R_2 = NH_2

Treatment of 6-demethyl-6-deoxytetracycline (II) with N-bromosuccinimide in concentrated sulfuric acid at 0° yielded a single monobromo-6-demethyl-6-deoxytetracycline sulfate (III, found for $C_{21}H_{21}N_2O_7Br \cdot H_2SO_4 \cdot CH_3OH$: C, 42.5; H, 4.7; OCH_3, 5.0; $\lambda_{max}^{0.1N\ HCl}$ 270, 345 mμ, log ε 4.28, 4.08, $[\alpha]^{25}D$ −97°, R_f 0.82).[3] Analogies[4,5] to this electrophilic reaction on aromatic compounds suggested substitution in the D ring, which was supported by the absorption spectra and chemical behavior of the product. Convincing evidence for the exact assignment was obtained by carrying out the halogenation on 6-demethyl-6-deoxytetracycline labeled with tritium in the 7-position.[6] The displacement of tritium by bromine provided proof that the substituent occupied the 7-position.[7] Similarly, treatment of 6-demethyl-6-deoxytetracycline (II) with N-iodosuccinimide gave 7-iodo-6-demethyl-6-deoxytetracycline sulfate (IV, found for $C_{21}H_{21}N_2O_7I \cdot H_2SO_4 \cdot 0.5H_2O$: C, 39.1; H, 4.2; I, 19.2; $\lambda_{max}^{0.1N\ HCl}$ 230, 345 mμ, log ε 4.48, 4.12, $[\alpha]^{25}D$ +383°, R_f 0.91). Reaction of 6-deoxytetracycline (I) with either N-bromosuccinimide or N-iodosuccinimide yielded 7-bromo-6-deoxytetracycline sulfate (V, found for $C_{22}H_{23}N_2O_7Br \cdot H_2SO_4 \cdot H_2O$: C, 42.3; H, 4.7; Br, 13.0; $\lambda_{max}^{0.1N\ HCl}$ 268, 345 mμ, log ε 4.24, 4.10, $[\alpha]^{25}D$ −221°, R_f 0.80) or 7-iodo-6-deoxytetracycline sulfate (VI, found for $C_{22}H_{23}N_2O_7I \cdot H_2SO_4$: N, 3.8; S, 4.8; I, 19.5; $\lambda_{max}^{0.1N\ HCl}$ 240, 260, 345 mμ, log ε 4.26, 4.22, 4.08, $[\alpha]^{25}D$ −282°, R_f 0.91), respectively.

In contrast to halogenation, nitration of 6-demethyl-6-deoxytetracycline with potassium nitrate in concentrated sulfuric acid at 0° gave two mononitro isomers. Using the technique described above with tritium labeled starting material one of these isomers was proved to be 7-nitro-6-demethyl-6-deoxytetracycline (VII, found for $C_{21}H_{21}N_3O_9 \cdot 2H_2O$: C, 51.3; H, 5.8; N, 8.2; $\lambda_{max}^{0.1N\ HCl}$ 262, 350 mμ, log ε 4.35, 4.27, $[\alpha]^{25}D$ −442°, R_f 0.64). Since the groups attached to the aromatic ring of the molecule would direct electrophilic attack to the 7 and 9 positions, it was assumed that the isomer which retains the tritium label was 9-nitro-6-demethyl-6-deoxytetracycline (VIII, found for $C_{21}H_{21}N_3O_9$: C, 55.1; H, 5.2; N, 9.0; $\lambda_{max}^{0.1N\ HCl}$ 263, 360 mμ, log ε 4.42, 4.24, $[\alpha]^{25}D$ −131°, R_f 0.48). In a like manner, nitration of 6-deoxytetracycline (I) gave two isomers, but the ratio of 7-nitro-6-deoxytetracycline (IX)[8] to 9-nitro-6-deoxytetracycline (X) was smaller than in the 6-demethyl series and was attributed to the steric hindrance of the 6-methyl group. The 9-nitro-6-deoxytetracycline (X, found for $C_{22}H_{23}N_3O_9 \cdot C_4H_9OH \cdot H_2SO_4$: C, 47.8; H, 5.2; N, 6.9; $\lambda_{max}^{0.1N\ HCl}$ 260, 365 mμ, log ε 4.43, 4.23, $[\alpha]^{25}D$ −268°, R_f 0.58) was purified in sufficient quantities to be used in subsequent reactions.

Catalytic reduction of the nitro compounds with platinum yielded the corresponding amino derivatives, 7-amino-6-demethyl-6-deoxytetracycline (XI, found for $C_{21}H_{23}N_3O_7 \cdot 2HCl \cdot 3H_2O$: C, 45.4; H,

(1) J. R. D. McCormick, E. R. Jensen, P. A. Miller and A. P. Doerschuk, THIS JOURNAL, in press.
(2) C. R. Stephens, K. Murai, H. H. Reinhard, L. H. Conover and K. J. Brunings, *ibid.*, **80**, 5324 (1958).
(3) All optical rotations were determined at a concentration of 0.1–0.5% in 0.1 *N* sulfuric acid. R_f values were determined in the system 1 butanol/0.2 *M* phosphate buffer, *p*H 2.
(4) J. B. Menke, THIS JOURNAL, **44**, 141 (1925).
(5) H. Schmid, *Helv. Chim. Acta*, **29**, 1144 (1946).
(6) This material was prepared by the method of J. R. D. McCormick, *et al.* (see ref. 1) using 6-demethyltetracycline-7H[3] made by the method of T. Andre and S. Ullberg, THIS JOURNAL, **79**, 494 (1957).
(7) To our knowledge this is the first use of tritium replacement as a structure proof and we are indebted to Dr. E. F. Ullman for the suggestion of this elegant method.
(8) This material was characterized by paper strip chromatography, and the isomer ratio was estimated from the mixture.

6.0; N, 7.3; $\lambda_{max}^{0.1N\ HCl}$ 265, 350 mμ, log ε 4.34, 4.21, $[\alpha]^{25}D$ −191°, R_f 0.02), 9-amino-6-demethyl-6-deoxytetracycline (XII, found for $C_{21}H_{23}N_3O_7 \cdot 1.5H_2O$: C, 54.8; H, 5.8; N, 8.9; $\lambda_{max}^{0.1N\ HCl}$ 265, 350 mμ, log ε 4.33, 4.25, $[\alpha]^{25}D$ −212°, R_f 0.02), and 9 - amino - 6 - deoxytetracycline (XIII, found for $C_{22}H_{25}N_3O_7 \cdot C_4H_9OH \cdot 2H_2SO_4$: C, 43.7; H, 5.4; N, 6.2; $\lambda_{max}^{0.1N\ HCl}$ 265, 350 mμ, log ε 4.26, 4.17, $[\alpha]^{25}D$ − 211°, R_f 0.02).

Bromination and nitration of 9-amino-6-deoxytetracycline under the previously described conditions yielded 9-amino-7-bromo-6-deoxytetracycline (XIV, found for $C_{22}H_{24}N_3O_7Br \cdot H_2O \cdot 2H_2SO_4$: C, 36.0; H, 4.5; N, 10.9; $\lambda_{max}^{0.1N\ HCl}$ 265, 348 mμ, log ε 4.31, 4.07, $[\alpha]^{25}D$ −153°, R_f 0.44) and 9-amino-7-nitro-6-deoxytetracycline (XV, found for $C_{22}H_{24}N_4O_9 \cdot 2H_2SO_4$: C, 38.8; H, 4.7; N, 8.0; $\lambda_{max}^{0.1N\ HCl}$ 261, 348 mμ, log ε 4.32, 414, $[\alpha]^{25}D$ −300°, R_f 0.48), respectively. The position of the bromo and nitro groups in the aromatic ring was proved by the use of tritium labeled starting material.

The relative *in vitro* antibacterial activities of the compounds described in this paper are presented in Table I.

TABLE I

In Vitro ANTIBACTERIAL ACTIVITY IN % COMPARED TO 7-CHLOROTETRACYCLINE[a]

6-Deoxytetracycline (I)	18
6-Demethyl-6-deoxytetracycline (II)	40
7-Bromo-6-demethyl-6-deoxytetracycline (III)	60
7-Iodo-6-demethyl-6-deoxytetracycline (IV)	30
7-Bromo-6-deoxytetracycline (V)	30
7-Iodo-6-deoxytetracycline (VI)	14
7-Nitro-6-demethyl-6-deoxytetracycline (VII)	160
9-Nitro-6-demethyl-6-deoxytetracycline (VIII)	3
7-Nitro-6-deoxytetracycline (IX)	60[8]
9-Nitro-6-deoxytetracycline (X)	<1
7-Amino-6-demethyl-6-deoxytetracycline (XI)	21
9-Amino-6-demethyl-6-deoxytetracycline (XII)	40
9-Amino-6-deoxytetracycline (XIII)	14
9-Amino-7-bromo-6-deoxytetracycline (XIV)	35
9-Amino-7-nitro-6-deoxytetracycline (XV)	41

[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).

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THE INFRARED SPECTRA OF METAL CARBONYLATE IONS. BONDING CONSIDERATIONS

Sir:

The infrared spectra of various solid salts of $Co(CO)_4^-$, $Fe(CO)_4^=$ and $HFe(CO)_4^-$, of water solutions of these ions in the 5μ region, and of tetrahydrofuran and diglyme solutions of $Mn(CO)_5^-$ and $Co(CO)_4^-$ have been examined with prisms and small gratings. Averages of components split by crystal effects are given when only data on solids are available. The results are $Co(CO)_4^-$: 1886(vs), 555(s), 530(w); $Fe(CO)_4^=$: 1786(vs), 646(s), 556(m); $HFe(CO)_4^-$: 2015 (w), 1937(sh), 1897(vs), 693(m), 618(s), 594(m), 540(w), 513(?); $Mn(CO)_5^-$: 1898(vs), 1863(vs) 683(s), 659(s), 564(w), 511(m), 467(m) cm.$^{-1}$. The two stronger bands of $Co(CO)_4^-$ previously were reported by Friedel, *et al.*,[1] while those for $Fe(CO)_4^=$ and $HFe(CO)_4^-$ correspond, with several exceptions, to Raman lines recently found by Stammreich and co-workers.[2]

The C–O stretching frequencies in isoelectronic, isosteric series have significance in relation to a simplified molecular orbital model of the bonding.[3] Following the lead of Edgell and Gallup,[4] the "lone-pair" σ_{CO}, the π_{CO} and the π^*_{CO} orbitals of carbon monoxide and the 3d, 4s, and 4p orbitals of the metal are considered as starting orbitals. Consider the case of the $M(CO)_4$ species. Using symmetry and rough energy arguments, the lower energy or "B orbitals" of the molecular species consist of nine bonding orbitals plus three, nonbonding, π_{CO} orbitals. The five remaining occupied or "A orbitals" may be thought of as closing an electron shell. When the relative energies of the π^*_{CO} orbitals are so high that they make no contribution to the A subshell orbitals, the latter will be antibonding between the metal and the CO groups. But with energy decrease, the addition of π^*_{CO} character to the A orbitals may be expected to result in energy stabilization of this subshell, a reduction in metal-CO antibonding character, and the appearance of C–O antibonding character. Thus, the π^*_{CO} character of the A orbitals is an important factor in the bonding description.

The C–O stretching frequencies in $Ni(CO)_4$, $Co(CO)_4^-$ and $Fe(CO)_4^=$ are 2057, 1886 and 1786 cm.$^{-1}$, respectively; the values at 1898 and 1863 for $Mn(CO)_5^-$ correspond to 2034 and 2014 for $Fe(CO)_5$, while 1897, 1937 for $HFe(CO)_4^-$ are shifted from 2043, 2062 cm.$^{-1}$ for $HCo(CO)_4$. These large frequency decreases with anionic charge result from increasing π^*_{CO} character of the A orbitals. It may be estimated that the *drop* in the C–O force constant factor, $k_{CO} - k_{CO,CO}$, is about 4.4 md./A. in going from $Ni(CO)_4$ to $Fe(CO)_4^=$. This corresponds to a *substantial* increase in π^*_{CO} stabilization and suggests that the order of the Ni–C bond may not be as large as sometimes estimated.

These results imply that the C–O stretching frequencies are an important diagnostic for bonding character in similar molecules. These considerations have been applied to such molecules as $Co(CO)_3NO$, $Fe(CO)_2(NO)_2$, $Fe(CO)_4I_2$, $HgFe(CO)_4$, the hydrides, *etc.*

The spectra of $Fe(CO)_4^=$ and $Co(CO)_4^-$ are consistent with tetrahedral structures; that of Mn-

(1) R. Friedel, I. Wender, S. Shufler and H. Sternberg, THIS JOURNAL, **77**, 3951 (1955).

(2) H. Stammreich and co-workers, private communication.

(3) W. F. Edgell, Abstracts, 134th Meeting Am. Chem. Soc., Chicago, Ill., Sept., 1958; talks before various A.C.S. local sections 1958-1959.

(4) W. F. Edgell and G. Gallup, THIS JOURNAL, **78**, 4188 (1956).