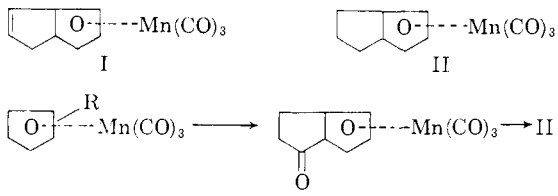
carbonyl), and [1,2-(trimethylene)-cyclopentadienyl]-manganese tricarbonyl, respectively. An independent synthesis was undertaken to confirm the structures.



Accordingly [(chloroformyl)-cyclopentadienyl]-manganese tricarbonyl[3] (III) was treated with lithium tri-*t*-butoxyaluminohydride[4] to give [(formyl)-cyclopentadienyl]-manganese tricarbonyl (IV). The IV was condensed with malonic acid to give [(2-carboxyvinyl) - cyclopentadienyl]-manganese tricarbonyl (V). V was reduced over Raney nickel to give [(2-carboxyethyl)-cyclopentadienyl]-manganese tricarbonyl (VI). VI was cyclized with polyphosphoric acid to yield [1,2-(1 - oxo - trimethylene) - cyclopentadienyl] - manganese tricarbonyl (VII). VII was reduced with zinc and hydrochloric acid to yield II. Comparison of this material with that obtained by reduction of I, by infrared, mixed melting point, vapor phase chromatography and X-ray diffraction showed them to be identical in every respect. Since there is only one possible position for the double bond in I, this also proves the structure of I.

(3) Prepared by the method of J. Kozikowski, unpublished work.

(4) H. C. Brown and R. F. McFarlin, THIS JOURNAL, **80**, 5372 (1958).

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16-FLUORINATED CORTICOIDS. II. 16α-FLUOROPREDNISOLONE AND 9α,16α-DIFLUOROPREDNISOLONE DERIVATIVES

Sir:

This report is a preliminary account of the synthesis of 16-fluoro cortical hormones, a unique class of biologically active steroids.

21-Acetoxy-11β-hydroxy-1,4,17(20)-pregnatrien-3-one (Ia)[1] was oxidized by selenium dioxide in aqueous dioxane to form 21-acetoxy-11β,16α-dihydroxy-1,4,17(20)-pregnatrien-3-one (II), m.p. 179–181°, $[\alpha]_D$ +83° (chf.). The oily 16-acetate (III) obtained from II, when treated with N-methylmorpholine oxide-peroxide[2] and a catalytic amount of osmium tetroxide afforded the known 16α,21-diacetoxy-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (IV)[3], m.p. 162–165°. This compound was identical with that prepared by the osmium tetroxide hydroxylation of the Δ^{16}-20-ketone (XVII), *vide infra*. The position and stereochemistry of the new hydroxyl introduced into I was thus established as 16α. With thionyl chloride–tributylamine, II yielded 20-chloro-21-acetoxy-11β-hydroxy-1,4,16-pregnatrien-3-one (V), m.p. 160–161°, $[\alpha]_D$ + 65° (chf.)[4]. Chromic acid oxidation of the 16α,17α-diol (VI), m.p. 223–224°, $[\alpha]_D$ + 2° (chf.), formed by treatment of V with osmium tetroxide, yielded 21-acetoxy-20-chloro - 3,11,17 - trioxo - 16,17 - seco - 1,4 - pregnadien-16-oic acid (VII), m.p. 238–241°, λ_{max}^{EtOH} 238 mμ (15,000). Titration with 0.1 *N* sodium hydroxide quantitatively transformed V to the 20,21-oxide (VIIIa), m.p. 205–210°, $[\alpha]_D$ + 125° (chf.). In a similar manner 21-acetoxy-11β-hydroxy-4,17(20)-pregnadien-3-one (Ib)[5] was converted to 11β - hydroxy - 20,21 - oxido - 4,16 - pregnadien - 3 - one (VIIIb), m.p. 154–155°, $[\alpha]_D$+212° (chf.). Lithium aluminum hydride reduction of VIIIb and then oxidation with manganese dioxide led to the isolation of approximately equal amounts of 11β,21-dihydroxy-4,16-pregnadien-3-one (IX), m.p. 151–153° and 11β-hydroxy-4,16-pregnadiene-3,20-dione (X), m.p. 171–173°, λ_{max}^{EtOH} 241 mμ (25,200). The latter compound was oxidized to the known 3,11,20-trione[6]. This sequence established the structure of the 20,21-oxide, VIIIb, and by analogy the $\Delta^{1,4}$-analog, VIIIa.

When the oxide VIIIa was treated with hydrogen fluoride and the product acylated, a mixture was obtained from which 20-fluoro-21-acetoxy-11β-hydroxy-1,4,16-pregnatrien-3-one XI, m.p. 173–178°, $[\alpha]_D$+80° (chf.) and 16α-fluoro-21-acetoxy-11β-hydroxy-1,4,17(20)-pregnatrien-3-one XII, m.p. 190–191°, $[\alpha]_D$+59° (chf.) were isolated. Evidence of the presence of the 16β-fluoro-isomer XIII was obtained, but this compound was not isolated. Ozonization of XI yielded the 16,17-seco-keto acid XIV, m.p. 221–224° while similar treatment of XII afforded 16α-fluoro-11β-hydroxy-4-androstene-3,17-dione XV, m.p. 197–198°, $[\alpha]_D$+135° (chf.). A mixture of 20- and 16-fluoro compounds was also obtained when the 20-chloro compound V was treated with silver fluoride under a variety of conditions; however, the main product of this reaction was the 20-hydroxy compound XVI, m.p. 194–198°, $[\alpha]_D$+92° (chf.). Manganese dioxide oxidation of XVI afforded the 20-ketone XVII, m.p. 208–209°, $[\alpha]_D$+146°, λ_{max}^{EtOH} 242 mμ (23,750), which when treated with osmium tetroxide with subsequent acylation yielded the known tetrol (IV).

The mixture of 16-fluorides XII and XIII when treated with N-methylmorpholine oxide-peroxide and a catalytic amount of osmium tetroxide gave 16α-fluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione XVIII, m.p. 219–220°, and small amounts of the 16β-isomer XIX, m.p. 174–177°, identical with that obtained by another

(1) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, THIS JOURNAL, **77**, 4438 (1955).

(2) W. P. Schneider and A. R. Hanze, U. S. 2,769,823 (November 6, 1956).

(3) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, THIS JOURNAL, **81**, 1689 (1959).

(4) *Cf.* R. E. Ireland, T. I. Wrigley and W. G. Young, *ibid.*, **80**, 4604 (1958), who also noted that thionyl chloride–tributylamine, conditions that usually favor an SN2 process, in certain cases yielded the rearranged chloride by way of an SNi' mechanism.

(5) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein and R. W. Jackson, *ibid.*, **77**, 4436 (1955).

(6) B. J. Magerlein, D. A. Lyttle, R. H. Levin, *J. Org. Chem.*, **20**, 1709 (1955).

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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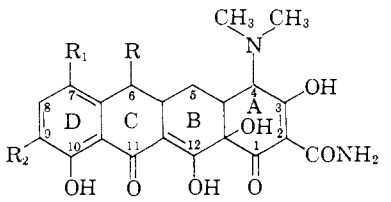
6-DEOXYTETRACYCLINES. I. CHEMICAL MODIFICATION BY ELECTROPHILIC SUBSTITUTION

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. Rennhard, 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.