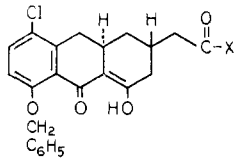
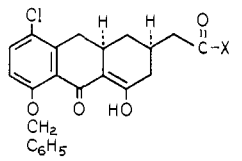
tion into the *syn* acid IVa (m.p. 197.5–200°; found: C, 66.57; H, 5.54; Cl, 8.83; λ_{max}^{MeOH} 342 mμ, log ε 4.14) and the *anti* acid IVb (m.p. 179–181°; found: C, 66.58; H, 5.41; λ_{max}^{MeOH} 342 mμ, log ε 4.14).

Relative stereochemical assignments were made on the basis that cyclization to *syn* product IVa occurred more rapidly and in higher yield (30–35%) than did closure to *anti* isomer IVb (10–15%),[2] and on the fact that treatment of IVa with diazomethane produced the previously described *syn* ester IVc.[1]



IVb X = GH
Vb X = $CH(COOC_2H_5)_2$



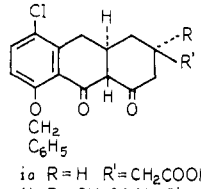
IVa X = OH
IVc X = OCH_2
Va X = $CH(COOC_2H_5)_2$

Conversion of *syn* acid IVa to acylmalonate Va, and then cyclization with sodium hydride in refluxing toluene gave the tetracyclic ester VI[3,4] in 30% yield (m.p. 151–154°; found: C, 66.01; H, 5.54; $\lambda_{max}^{0.1M\ Na_2B_4O_7}$, 440, 340, 265 mμ, log ε, 4.20, 3.98, 4.05). Hydrogenolysis of the benzyl group over 10% Pd/C yielded phenol VII (m.p. 162–4°, $\lambda_{max}^{0.1M\ Na_2B_4O_7}$, 450, 270 mμ, log ε, 4.39, 4.05). Fusion of the latter with ammonium formate at 140°, and hydrolysis with hydrochloric acid led in low yield to racemic amide I (λ_{max}^{KBr} 2.93, 6.30, 6.86, 7.66, 8.61, 12.10, 12.60 μ, $\lambda_{max}^{0.001N\ NaOH(MeOH)}$ 495, 469, 375, 262 mμ).

Natural 6-demethyl-7-chlorotetracycline[5] was converted to the 6-deoxy derivative by catalytic reduction.[6] Zinc dust reduction[7] of the dimethylamino and 12a hydroxyl groups gave optically active amide I (found: C, 58.69; H, 4.64; N, 3.88). Comparison of this material with the synthetic product by paper chromatography, infrared and ultraviolet spectroscopy demonstrated the chemical identity of the two samples.[8]

This work, in conjunction with the recently reported techniques for 12a hydroxylation,[9] leaves the introduction of the dimethylamino group as the main barrier to the total synthesis of a tetracycline having full biological activity. In so far as the stereochemistry of the tetracyclines parallels that of the 6-demethyltetracyclines, the present synthesis serves to buttress the stereochemical conclusions of Woodward[10] and Pepinsky[11] based on degradative and X-ray diffraction studies.

(2) A total of six conformations can be drawn for the transition states leading to IVa and IVb. Four of these each possess a minimum of two 1,3-diaxial carbon-hydrogen interactions and may be regarded as unlikely. For the remaining two, which would lead to intermediate diketones ia and ib, that giving ia involves one less 1,3-diaxial carbon-hydrogen interaction than that giving ib, hence formation of ia and thus IVa should be kinetically favored.



ia R = H R' = CH_2COOH
ib R = CH_2COOH R' = H

(3) Zinc dust distillation of the ester gave naphthacene.

(4) Spectroscopic evidence indicates that, under identical reaction conditions, the *anti* acylmalonate Vb fails to yield a tetracyclic compound.

(5) (a) J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen and A. P. Doerschuk, THIS JOURNAL, **79**, 4561 (1957); (b) J. S. Webb, R. W. Broschard, D. B. Cosulich, W. J. Stein and C. F. Wolf, *ibid.*, **79**, 4563 (1957); (c) J. H. Boothe, A. Green, J. P. Petisi, R. G. Wilkinson and C. W. Waller, *ibid.*, **79**, 4564 (1957).

(6) J. R. D. McCormick and E. Jensen, private comm.

(7) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **74**, 4976 (1952); **76**, 3568 (1954).

(8) We are indebted to W. Fulmor and associates for the spectroscopic data, L. Brancone and staff for the microanalytical data and to R. Livant for the chromatographic work.

(9) (a) C. E. Holmlund, W. W. Andres and A. J. Shay, THIS JOURNAL, **81**, 4748 (1959); **81**, 4750 (1959); (b) H. Muxfeldt and A. Kreutzer, *Naturwissenschaften*, **46**, 204 (1959).

(10) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

(11) S. Hirokawa, Y. Okaya, F. M. Lovell and R. Pepinsky, Abst. of Amer. Cryst. Assoc. Meeting, Cornell University, July, 1959, p. 44.

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RECEIVED JANUARY 25, 1960

π-DIHYDROPENTALENYL MANGANESE TRICARBONYL

Sir:

This communication describes the novel reactions of acetylene and cycloöctatetraene with manganese carbonyl. Treatment of a tetrahydrofuran solution of manganese carbonyl with acetylene at 600 p.s.i. and 150° for five hours gave a 40% yield of a yellow oil, I, b.p. 144° (18 mm.). *Anal.* Calcd. for $C_{11}H_7MnO_3$: C, 55.5; H, 2.88; Mn, 22.7; mol. wt., 242. Found: C, 55.4; H, 3.2; Mn, 22.2; mol. wt., 231. Treatment of a tetrahydrofuran solution of methylmanganese pentacarbonyl with acetylene under similar conditions gave a 27% yield of I.

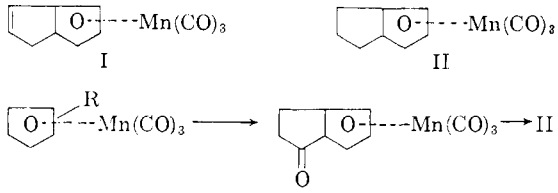
Compound I absorbed one mole of hydrogen over Raney nickel catalyst to give compound II. *Anal.* Calcd. for $C_{11}H_9MnO_3$: C, 54.2; H, 3.7; Mn, 22.5. Found: C, 54.3; H, 3.9; Mn, 22.4. Compound I was oxidized in low yield by permanganate to a diacid, neutralization equivalent 160, in which the manganese was still complexed. Reaction of cycloöctatetraene with manganese carbonyl in an autoclave also gave a small yield of compound II.

Compound I was diamagnetic[1] and the nuclear magnetic resonance spectrum showed shifts at 191, 277, and 382 c.p.s. from the tetramethylsilane reference, with the relative areas under the peaks being 2:3:2.[2] The 277 peak is in the region where protons on a cyclopentadiene ring complexed to a manganese tricarbonyl moiety absorb. On the basis of these data I and II were postulated to be [1,2-(propenylene)-cyclopentadienyl]-manganese tricarbonyl, (π-dihydropentalenyl manganese tri-

(1) We wish to thank Dr. Stanley Kirschner of Wayne State University for making this measurement.

(2) We are indebted to Dr. James Shoolery and Mr. Roy Johnson of Varian Associates for these measurements, taken on a 60 mc. high resolution spectrometer.

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 S_N2 process, in certain cases yielded the rearranged chloride by way of an S_Ni' 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).