188–190° (*Anal.* Found: C, 73.10; H, 9.07). The acetate of I, m.p. 140–142°, $[\alpha]_D$ + 19[6], on bromination[7] with N-bromosuccinimide in carbon tetrachloride afforded methyl 16α-bromo-3β-hydroxy-11-keto-5α-pregn-17(20)-[*cis*]-en-21-oate acetate (II),[8] m.p. 197–200°, $[\alpha]$ −213° (*Anal.* Found: C, 59.68: H, 6.93; Br, 16.68). When II was heated under reflux with silver fluoride[9] in acetonitrile an excellent yield of methyl 16β-fluoro-3β-hydroxy-11-keto-5α-pregn-17(20)-[*cis*]-en-21-oate acetate (III), m.p. 231–232°, $[\alpha]$ + 33° (*Anal.* Found: C, 68.77; H, 7.67; F, 4.6), was obtained. Solvolysis of the acetate by ester interchange with methanol and boron trifluoride etherate, then oxidation of the crude product with chromic acid[10] gave methyl 16β-fluoro-3,11-diketo-5α-pregn-17(20)-[*cis*]-en-21-oate (IV), m.p. 213–214°. (*Anal.* Found: C, 69.71; H, 7.98; F, 4.82.) Ketalization of IV with ethylene glycol gave the corresponding 3-ethylenedioxy derivative, m.p. 255–260°. Lithium aluminum hydride reduction of the ketal in tetrahydrofuran at 0°, acetylation of the resulting 21-alcohol and ketal hydrolysis gave 11β,21-dihydroxy-16β-fluoro-5α-pregn-17(20)-[*cis*]-en-3-one 21-acetate (V), m.p. 137–139° (*Anal.* Found: C, 70.38; H, 8.60; F, 4.64). Oxidation of V with N-methylmorpholine oxide-peroxide[11] and a catalytic amount of osmium tetroxide gave 16β-fluoro-11β,17α,21-trihydroxy-5α-pregnane-3,20-dione 21-acetate (VI), m.p. 190–193° (*Anal.* Found: C, 65.49; H, 7.86; F, 4.29).

The β-orientation of the 16-fluoro substituent was established in the following manner. The amorphous 21-alcohol obtained by solvolysis of VI was converted[12] *via* the mesylate and iodide to 11β,17α-dihydroxy-16β-fluoro-5α-pregnane-3,20-dione (VII), m.p. 187–188° (*Anal.* Found: C, 69.56; H, 9.35; F, 5.88.) Treatment of VII with potassium hydroxide in aqueous methanol gave amorphous 11β-hydroxy-16,17α-epoxy-5α-pregnane 3,20-dione which was oxidized with N-bromoacetamide to 16,17α-epoxy-5α-pregnane-3,11,20-trione (VIII), m.p. 189–191° (*Anal.* Found: C, 73.30; H, 8.38), identical with an authentic sample prepared by the chromic acid oxidation of 3β-hydroxy-16,17α-epoxy-5α-pregnane-11,20-dione.[13]

Dehydrogenation of VI with selenium dioxide[14] afforded 16β-fluoroprednisolone acetate (IX), m.p. 179–181°, λ_{max} 243 mμ (ε 15,400) (*Anal.* Found: C, 65.40; H, 7.17; F, 4.58). By application of the well-known sequence for introducing the 9-fluoro substituent,[15] 9α,16β-difluoroprednisolone acetate (X) was obtained as a mono-acetone solvate, m.p. 110–115°, λ_{max} 239 mμ (ε 15,550) (*Anal.* Found: C, 63.03; H, 7.08; F, 7.5). Bromination of VI in dioxane afforded the 2,4-dibromo derivative (*Anal.* Found: Br, 27.12) which was treated with sodium iodide in refluxing acetone. The crude product after stirring with zinc and acid was purified through its Girard derivative[16] to produce 16β-fluorohydrocortisone acetate (XI), m.p. 160–161°, λ_{max} 241 mμ (ε 15,750) (*Anal.* Found: C, 65.83; H, 7.91).

Bioassays indicate that 9α,16β-difluoroprednisolone acetate is three times as active as hydrocortisone by glycogen deposition[17] and does not induce sodium retention at a dose of 500γ in the rat, whereas 9α-fluoroprednisolone acetate produces marked sodium retention.[12]

(6) Rotations were determined in chloroform using the sodium-D line. Ultraviolet spectra are of ethanolic solutions of the compounds.

(7) V. Černý and F. Sörm, *Coll. Czech. Chem. Comm.*, **22**, 85 (1957).

(8) The configuration about the 17(20)-bond of II–V is believed to be *cis*, although this has not been unequivocally established. The α-orientation was assigned to the bromo-substituent by analogy with 17-ketones. The ΔM_D for 16α-bromination of 17-ketones is strongly negative; *cf.* C. W. Shoppee, R. H. Jenkins and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958).

(9) A solution of silver fluoride prepared from silver oxide and anhydrous hydrogen fluoride in acetonitrile gave better results than commercial solid silver fluoride.

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

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(13) J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 5615 (1952).

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(16) R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney and G. H. Phillipps, *J. Chem. Soc.*, 1529 (1958).

(17) R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955).

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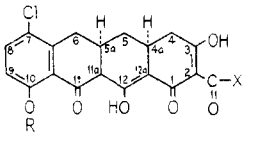
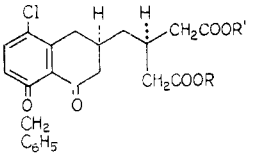
RECEIVED JANUARY 14, 1960

TOTAL SYNTHESIS OF TETRACYCLINES. II. STEREOSPECIFIC SYNTHESIS OF (±)-DEDIMETHYLAMINO-6-DEMETHYL-6,12a-DIDEOXY-7-CHLOROTETRACYCLINE

Sir:

A previous communication from these laboratories has described the synthesis of (±)-dedimethylamino-12a-deoxy-6-demethylanhydrochlorotetracycline.[1] We now report a total synthesis of (±)-dedimethylamino-6-demethyl-6,12a-dideoxy-7-chlorotetracycline I by a stereospecific route which illuminates the skeletal stereochemistry of this family of antibiotics.





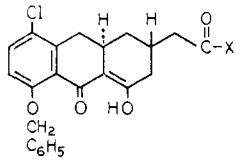
I R = H X = NH_2 II R = R′ = H
VI R = $CH_2C_6H_5$ X = OC_2H_5 IIIa R = CH_3 R′ = H
VII R = H X = OC_2H_5 IIIb R = H R′ = CH_3

Treatment of the anhydride (m.p. 192–193°; found: C, 66.64; H, 5.32; Cl, 8.60) of the glutaric acid II[1] with sodium methoxide led to a crystalline mixture of approximately equal proportions of the diastereomeric monoesters IIIa and IIIb. Cyclization of this mixture with sodium hydride in refluxing toluene gave the corresponding stereoisomeric tricyclic acids, separable by crystalliza-

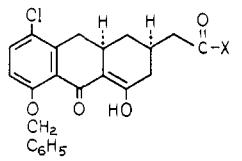
(1) (a) J. H. Boothe, A. S. Kende, T. L. Fields and R. G. Wilkinson, THIS JOURNAL, **81**, 1006 (1959). (b) A recent preliminary report by H. Muxfeldt, *Abst. of 17th Int. Cong. of Pure and Appl. Chem.*, Munich, Sept. 1959, Vol. II, p. 19, has described the total synthesis of dedimethylaminoanhydrochlorotetracycline. Also see H. Muxfeldt, *Ber.*, **92**, 3122 (1959).

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 = $CH(COOC_2H_5)_2$



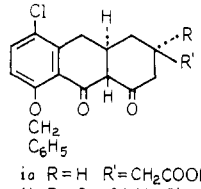
IVa X = OH
IVc X = OCH_2
Va X = $CH(COOC_2H_5)_2$

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.