

188–190° (*Anal.* Found: C, 73.10; H, 9.07). The acetate of I, m.p. 140–142°, $[\alpha]_D + 19^\circ$, on bromination⁷ with N-bromosuccinimide in carbon tetrachloride afforded methyl 16 α -bromo-3 β -hydroxy-11-keto-5 α -pregn-17(20)-[*cis*]-en-21-oate acetate (II),⁸ m.p. 197–200°, $[\alpha] - 213^\circ$ (*Anal.* Found: C, 59.68; H, 6.93; Br, 16.68). When II was heated under reflux with silver fluoride⁹ in acetonitrile an excellent yield of methyl 16 β -fluoro-3 β -hydroxy-11-keto-5 α -pregn-17(20)-[*cis*]-en-21-oate acetate (III), m.p. 231–232°, $[\alpha] + 33^\circ$ (*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 acid¹⁰ gave methyl 16 β -fluoro-3,11-diketo-5 α -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 11 β ,21-dihydroxy-16 β -fluoro-5 α -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-peroxide¹¹ and a catalytic amount of osmium tetroxide gave 16 β -fluoro-11 β ,17 α ,21-trihydroxy-5 α -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 converted¹² *via* the mesylate and iodide to 11 β ,17 α -dihydroxy-16 β -fluoro-5 α -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 11 β -hydroxy-16,17 α -epoxy-5 α -pregnane-3,20-dione which was oxidized with N-bromoacetamide to 16,17 α -epoxy-5 α -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 3 β -hydroxy-16,17 α -epoxy-5 α -pregnane-11,20-dione.¹³

Dehydrogenation of VI with selenium dioxide¹⁴ afforded 16 β -fluoroprednisolone acetate (IX), m.p.

179–181°, $\lambda_{\max}$ 243 m μ (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 9 α ,16 β -difluoroprednisolone acetate (X) was obtained as a mono-acetone solvate, m.p. 110–115°, $\lambda_{\max}$ 239 m μ (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 derivative¹⁶ to produce 16 β -fluorohydrocortisone acetate (XI), m.p. 160–161°, $\lambda_{\max}$ 241 m μ (ϵ 15,750) (*Anal.* Found: C, 65.83; H, 7.91).

Bioassays indicate that 9 α ,16 β -difluoroprednisolone acetate is three times as active as hydrocortisone by glycogen deposition¹⁷ and does not induce sodium retention at a dose of 500 γ in the rat, whereas 9 α -fluoroprednisolone acetate produces marked sodium retention.¹²

(15) J. Fried and E. F. Sabo, *THIS JOURNAL*, **76**, 1455 (1954).

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

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RESEARCH DIVISION
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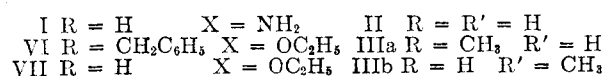
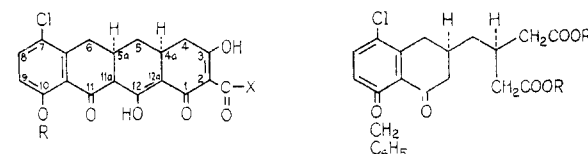
DONALD E. AYER
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RECEIVED JANUARY 14, 1960

TOTAL SYNTHESIS OF TETRACYCLINES. II. STEREOSPECIFIC SYNTHESIS OF ($\pm$)-DEDIMETHYLAMINO-6-DEMETHYL- 6,12 α -DIDEOXY-7-CHLOROTETRACYCLINE

Sir:

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



Treatment of the anhydride (m.p. 192–193°; found: C, 66.64; H, 5.32; Cl, 8.60) of the glutaric acid II¹ 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-

(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. Šorm, *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 16 α -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).

(11) W. F. Schneider and A. R. Hanze, U. S. Patent 2,769,823.

(12) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *THIS JOURNAL*, **77**, 4181 (1955).

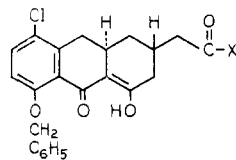
(13) J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 5615 (1952).

(14) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(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).

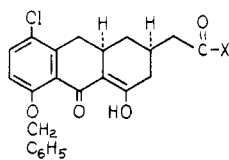
tion into the *syn* acid IVa (m.p. 197.5–200°; found: C, 66.57; H, 5.54; Cl, 8.83; $\lambda_{\text{max}}^{\text{MeOH}}$ 342 m μ , log ϵ 4.14) and the *anti* acid IVb (m.p. 179–181°; found: C, 66.58; H, 5.41; $\lambda_{\text{max}}^{\text{MeOH}}$ 342 m μ , log ϵ 4.14).

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(COOC₂H₅)₂



IVa X = OH

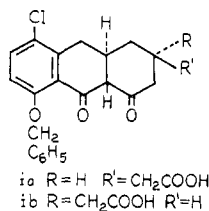
IVc X = OCH₃

Va X = CH(COOC₂H₅)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; $\lambda_{\text{max}}^{0.1M \text{ Na}_2\text{B}_4\text{O}_7}$, 440, 340, 265 m μ , log ϵ , 4.20, 3.98, 4.05). Hydrogenolysis of the benzyl group over 10% Pd/C yielded phenol VII (m.p. 162–4°, $\lambda_{\text{max}}^{0.1M \text{ Na}_2\text{B}_4\text{O}_7}$, 450, 270 m μ , 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 ($\lambda_{\text{max}}^{\text{KBr}}$ 2.93, 6.30, 6.86, 7.66, 8.61, 12.10, 12.60 μ , $\lambda_{\text{max}}^{0.001N \text{ NaOH(MeOH)}}$ 495, 469, 375, 262 m μ).

Natural 6-demethyl-7-chlorotetracycline⁵ was converted to the 6-deoxy derivative by catalytic reduction.⁶ Zinc dust reduction⁷ 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

(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' = CH₂COOH

ib R = CH₂COOH 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).

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 Woodward¹⁰ and Pepinsky¹¹ based on degradative and X-ray diffraction studies.

(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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π -DIHYDROPENTALENYL MANGANESE TRICARBONYL

Sir:

This communication describes the novel reactions of acetylene and cyclooctatetraene 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 C₁₁H₇MnO₃: 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 C₁₁H₉MnO₃: 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 cyclooctatetraene with manganese carbonyl in an autoclave also gave a small yield of compound II.

Compound I was diamagnetic¹ 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.