Acetolysis of *trans*-4-Methoxycyclohexyl-1-*t* Tosylate.—*trans*-4-Methoxycyclohexyl-1-*t* tosylate (41.3 g., 0.145 mole, m.p. 66.4–67.2°, 2.62 ± 0.05 × 10^6 d.p.m./mmole) was solvolyzed in glacial acetic acid (500 ml., distilled from 10% acetic anhydride) containing sodium acetate (23.6 g.) and acetic anhydride (29.6 g.) at 74.98 ± 0.02° for 57.75 hours. The acetic acid was neutralized with aqueous sodium carbonate (1000 ml., 8.0 *M*) and sodium bicarbonate (81.4 g., 0.969 mole). The aqueous solution was continuously extracted with ether and the ethereal solution was dried over sodium sulfate–sodium carbonate. Distillation at reduced pressure yielded 4-methoxycyclohexene (b.p. 61–65° (77 mm.), 1.22 g., 7.5% yield, 2.33 ± 0.3 × 10^6 d.p.m./mmole) and 4-methoxycyclohexyl acetate (b.p. 85–86° (7 mm.), 7.52 g., 30.12% yield, 2.71 ± 0.05 × 10^6 d.p.m./mmole). The infrared spectra of these materials were identical with authentic samples.

Degradation of Solvolysis Products. (a) Oxidation of 4-Methoxycyclohexene-1-*t*.—4-Methoxycyclohexene-1-*t* (1.00 g., 1.30 × 10^5 d.p.m./mmole which was prepared by 20-fold dilution of the olefin above) in isoöctane (5 ml.) and water (25 ml.) was oxidized by dropwise addition of aqueous sodium permanganate (5.23 g., 30 ml.) below 18° under a carbon dioxide atmosphere. After one hour unreacted sodium permanganate was destroyed by addition of technical grade ether. Manganese dioxide was removed by filtration and washed with aqueous sodium hydroxide. The solution was adjusted to *p*H 1 and continuously extracted with ether. After removal of the ether under reduced pressure the crude β-methoxyadipic acid (1.00 g., 63%) was recrystallized seven times from hexane (m.p. 88.8–90.0°, Koefler hot-stage; 1850 d.p.m./mmole, 1.42% activity). After ten crystallizations the specific activity was zero; calcd. 88.09, found 88.60.

(b) Saponification of 4-Methoxycyclohexyl-1,4-*t* Acetate.—4-Methoxycyclohexyl-1,4-*t* acetate (6.35 g., 2.71 ± 0.05 × 10^6 d.p.m./mmole) from the acetolysis products was saponified with methanolic potassium hydroxide in the usual manner to yield a mixture of *cis*- and *trans*-4-methoxycyclohexanol-1,4 *t* (71% *trans* isomer by infrared analysis, b.p. 100.8–101.0° (13 mm.), 3.502 g., 72.9% yield, 2.63 ± 0.02 × 10^6 c.p.m./mmole).

(c) Oxidation of *cis–trans*-4-Methoxycyclohexanol-1,4-*t*.—The *cis–trans*-4-methoxycyclohexanol-1,4-*t* (0.913 g., 2.63 ± 0.02 × 10^6 d.p.m./mmole) was oxidized with chromium trioxide (14.92 meq.) in acetone (10 ml.) as before. The crude ketone was purified on Woelm 3 alumina. 4-Methoxycyclohexanone-4-*t* (0.591 g., 65.7%) was rechromatographed to afford material whose infrared spectrum was identical with authentic 4-methoxycyclohexanone. The specific activity was 0.80 ± 0.02 × 10^6 d.p.m./mmole.

(d) Separation of trans-4-Methoxycyclohexanol-1,4-*t*.—4-Methoxycyclohexanol-1,4-*t* (2.44 g., 2.63 ± 0.02 × 10^6 d.p.m./mmole) was converted to the hydrogen phthalate ester (3.4 g., 0.0122 mole, 65.2%) in the usual way. The ester was recrystallized three times from benzene (m.p. 149.8–150.4°) and saponified in aqueous sodium hydroxide. *trans*-4-Methoxy-cyclohexanol-1,4-*t* (0.888 g., 74.5%, b.p. 102° (13 mm.), 2.55 ± 0.01 × 10^6 c.p.m./mmole), having an infrared spectrum identical with authentic material, was isolated by fractional distillation.

(e) Oxidation of *trans*-4-Methoxycyclohexanol-1,4-*t*.—*trans*-4-Methoxycyclohexanol-1,4-*t* (0.664 g., 2.55 ± 0.10 × 10^6 d.p.m./mmole) was oxidized as before. The crude ketone was purified by chromatography and distillation through a short column at reduced pressure to yield 4-methoxycyclohexanone-4-*t* (0.477 g., 56.0%, 1.13 ± 0.01 × 10^6 d.p.m./mmole) having an infrared spectrum identical with authentic material.

(f) 2,6-Dibenzylidene-4-methoxycyclohexanone-4-*t*.—A diluted sample of 4-methoxycyclohexanone-4-*t* (0.116 g., 2.24 × 10^5 d.p.m./mmole), water (2 ml.), ethanol (0.5 ml., 95%), sodium hydroxide (0.15 g.), and freshly distilled benzaldehyde (0.36 g., 0.0034 mole, b.p. 90° (42 mm.)) was stirred at room temperature for 27 hours. Water (10 ml.) was added; the precipitate was collected and crystallized four times from aqueous ethanol to yield 2,6-dibenzylidene-4-methoxycyclo-hexanone-4-*t* (0.10 g., 36.4%, m.p. 118.4–118.8°). After seven crystallizations, m.p. 119.0–119.2°, the specific activity was 2.09 ± 0.20 × 10^5 d.p.m./mmole and after ten crystallizations, m.p. 119.2–119.3°, 2.13 ± 0.20 × 10^5 d.p.m./mmole. *Anal.* Calcd. for $C_{21}H_{18}O_2$: C, 82.86; H, 6.62. Found: C, 83.03; H, 6.47.

Radioassay.—The control oxidation product (4-methoxycyclohexanone) and its parent alcohol were counted with a Tracerlab model CE-1 liquid scintillation counter at the California Research Corporation. The remainder of the samples were counted on a locally fabricated liquid scintillation counter (using 2,5-diphenyloxazole) at Donner Laboratories. Samples were counted against background using both external and internal standards. Normal counting efficiencies of 20–35% were observed. Duplicate samples were counted in triplicate. The precision of these counts is indicated. The counting accuracy is the usual ±3%. Radioassay of 2,6-dibenzylidene-4-methoxycyclohexanone was made with added wave length shifter (1.2–1.8 mg./10 ml. of 2,2′-*p*-phenylenebis-[5-phenyloxazole]) and intensifier (523–543 mg./10 ml. of naphthalene). Counting efficiency was increased from 0.1 to 4% in these yellow solutions.

Acknowledgment.—We wish to express our appreciation to Mr. Irville M. Whittemore of the Donner Laboratory for his assistance with the counting procedures. We wish to thank Professor Melvin Calvin for making these facilities available to us. We wish also to thank Dr. Wm. A. Pryor and Dr. B. A. Fries of the California Research Corporation for their assistance with the early counting experiments.

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COMMUNICATIONS TO THE EDITOR

16-FLUORINATED CORTICOIDS. I. 16β-FLUOROHYDROCORTISONE ACETATE AND RELATED COMPOUNDS

Sir:

While 16β-bromo and 16β-chloro corticoids have been prepared by opening 16,17α-epoxy-20-keto steroids with hydrogen bromide[1] and hydrogen chloride,[2] efforts to prepare 16β-fluoro steroids by that route have been unsuccessful.[2] We now report the preparation of 16β-fluorohydrocortisone acetate and its Δ^1- and Δ^1-9α-fluoro derivatives by a different route. The reaction of 3β-hydroxy-5α-pregnane-11-20-dione[3] with diethyl oxalate in the presence of sodium methoxide gave the 21-ethoxyoxalyl derivative which was converted by means of bromination and Faworskii rearrangement with sodium methoxide[4] to methyl 3β-hydroxy-11-keto-5α-pregn-17(20)-[*cis*]-en-21-oate[5] (I), m.p.

(1) P. L. Julian, W. Cole, E. W. Meyer and B. M. Regan, THIS JOURNAL, **77**, 4601 (1955).

(2) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(3) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951).

(4) J. A. Hogg, P. F. Beal, A. H. Nathan and F. H. Lincoln, U. S. Patent 2,790,814.

(5) This compound was prepared earlier in these laboratories by R. W. Jackson in connection with another problem.

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).

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

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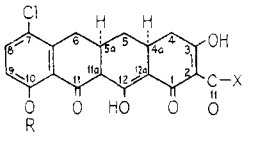
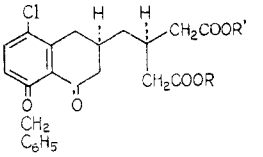
TOTAL SYNTHESIS OF TETRACYCLINES. II. STEREOSPECIFIC SYNTHESIS OF (±)-DEDIMETHYLAMINO-6-DEMETHYL-6,12a-DIDEOXY-7-CHLOROTETRACYCLINE

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).