(bp 60–110°); B, 5:3 C_6H_6–HOAc. All analytical samples gave combustion values within 0.4% of theory.

γ-(3,4-Dichlorophenyl)butyric Acid (11b).—Huang-Minlon reduction[12] of **10b** (prepared by ref 11 at 100°) gave 83% of crude product, bp 140–144° (0.1 mm), mp 48–64°, that was suitable for the next step. Three recrystallizations from EtOH–H_2O gave white crystals, mp 62–65°. *Anal.* ($C_{10}H_{10}Cl_2O_2$) C, H.

6,7-Dichloro-1-tetralone (12b).—To 184 g of polyphosphoric acid was added 18.4 g of P_2O_5 followed by 18.4 (78 mmoles) of **11b**. The mixture was stirred at 100° for 30 min, then cooled to 50° and diluted with 500 ml of ice water. The product was collected on a filter, washed with water, and recrystallized from EtOH–H_2O; yield 11.9 g (69%) of white crystals, mp 104–108°, tlc in solvent A. *Anal.* ($C_{10}H_8Cl_2O$) C, H, Cl.

Synthesized in the same way were **12d** [bp 77° (0.1 mm), mp 35° (lit.[9] mp 35°)], **12a** (mp 93–95°, lit.[18] mp 94°), and **12c** [bp 84–90° (0.05 mm), mp 44–46°]. *Anal.* ($C_{12}H_{14}O$) C, H.

6,7-Dichloronaphthyl-1-acethydrazide (15b) (Method A).—To a stirred suspension of 3.7 g (92 mmoles) of 60% suspension of NaH in mineral oil in 200 ml of dimethoxyethane (previously dried with molecular sieves) protected from moisture was added 18.8 g (84 mmoles) of triethyl phosphonoacetate. After being stirred at ambient temperature for 45 min, H_2 evolution was complete. A solution of 12 g (56 mmoles) of **12b** in 12 ml of dimethoxyethane was added, then the mixture was refluxed for 24 hr. The cooled reaction mixture was diluted with 400 ml of H_2O and extracted twice with $CHCl_3$. The combined extracts were washed with H_2O, dried with $MgSO_4$, and evaporated *in vacuo*. Distillation gave 13.1 g (88%) of **13b**, bp 127–130° (0.07 mm), as a colorless oil; tlc in solvent A showed one major, one minor, and two trace spots. The ir and nmr spectra were in agreement with this structure.

A solution of 14.9 g (61 mmoles) of *o*-chloranil and 15.7 g (56 mmoles) of **13b** in 700 ml of PhMe was refluxed for 4 hr; during this time the solution turned red, then orange. The solution was evaporated *in vacuo* and the residue dissolved in 700 ml of $CHCl_3$. The solution was washed successively with three 400-ml portions of 0.1 *N* KOH and two 150-ml portions of H_2O, then evaporated *in vacuo* leaving crude **14b** with the proper uv, ir, and nmr spectra.

A mixture of the crude **14b**, 350 ml of 85% $N_2H_4 \cdot H_2O$, and 110 ml of EtOH was refluxed for 4 hr, then evaporated to a small volume *in vacuo*. The solid was collected on a filter and washed extensively with H_2O. The crude product was stirred with 1.5 l. of 0.3 *N* HCl and 1 l. of MeOH until solution was essentially complete. The filtered solution was carefully made slightly basic with 5% $NaHCO_3$. The solid was collected on a filter, washed with H_2O, then recrystallized from MeOH–H_2O with the aid of charcoal; yield 3.56 g (24%), mp 198° on a Kofler–Heizbank since a melting point taken in the usual fashion showed no definite melting point due to decomposition. See Table II for additional data and other compounds prepared in this way.

6,7-Dichloro-1-naphthylmethylamine Hydrobromide (17b) (Method B).—A solution of 1.49 g (2.2 mmoles) of $C_6H_5CH_2OH$ in 270 ml of C_6H_6 was dried with molecular sieves, then 2.93 g (11 mmoles) of **15b** was added. The stirred suspension was saturated with NOCl. After being stirred 30 min at ambient temperature (N_2 evolved), the solution was refluxed 4.5 hr, then evaporated *in vacuo*. To the residual crude **16b** dissolved in 20 ml of HOAc was added a solution of 4.8 g of HBr gas in 40 ml of HOAc; CO_2 evolution was complete in 15 min and the product began to separate. The mixture was diluted with several volumes of Et_2O, then the product was collected on a filter and washed with Et_2O; yield, 2.18 g (65%) of crystals, mp 283–284 dec, suitable for the next step. For analysis a sample was recrystallized from EtOH–Et_2O; see Table II for additional data and other compounds prepared by this method.

6-(6,7-Dichloro-1-naphthylmethylamino)uracil (3) (Method C).—A mixture of 2.10 g (6.8 mmoles) of **17b**, 0.564 g (6.8 mmoles) of NaAc, 0.75 g (5.2 mmoles) o 6-chlorouracil,[3] and 78 ml of H_2O was refluxed with stirring for 48 hr. The hot solution was filtered and the product washed with H_2O; yield 0.82 g (45%). Recrystallization from DMF gave 0.22 g (12%) of product, mp >360°; tlc in solvent B showed one spot. See Table II for additional data and other compounds prepared by this method.

(18) J. v. Braun, A. Rohmer, H. Jungman, F. Zobel, L. Brauns, O. Bayer, A. Stuckenschmidt, and J. Reutter, *Ann.*, **451**, 1 (1926).

6-Fluorotetracyclines[1]

PANAYOTA BITHA, JOSEPH J. HLAVKA, AND JAMES H. BOOTHE

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

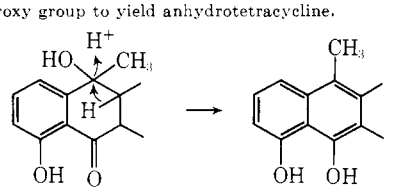
Received July 3, 1969

The reaction of 11a-halotetracyclines with liquid HF results in the replacement of 6-OH with F. When 11a-chloro-6-demethyltetracycline is treated with HF, the two possible 6-F stereoisomers were isolated. A tentative assignment of stereochemistry is given. When either 7,11a-dichloro-6-demethyltetracycline or 7,11a-dichlorotetracycline is treated with HF, only the more stable 6α-F isomers were isolated. In the latter case some previously reported 6-methylene derivative was also isolated.

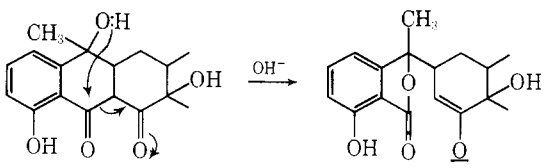
The lability of the 6-OH in the tetracycline molecule to both acid[2] and base degradation[3] has thwarted past efforts at successful replacement of this group with other than H.[4] Recently we have found that reaction of 11a-chloro-6-demethyltetracycline (**1**) in liquid HF yielded a mixture of two 6-fluoro stereoisomers, **2a,b** (Chart I). Dehydrochlorination of either of these stereoisomers afforded the same 5a(6)-anhydro-6-fluoro-6-demethyltetracycline (**3**). An nmr of this

(1) A preliminary report of this work was given at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968.

(2) 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, *J. Am. Chem. Soc.*, **76**, 3568 (1954); C. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, R. Broschard, and J. H. Williams, *ibid.*, **74**, 4981 (1952). Acid treatment of tetracycline results in a ready *trans* elimination of the 6-hydroxy group to yield anhydrotetracycline.

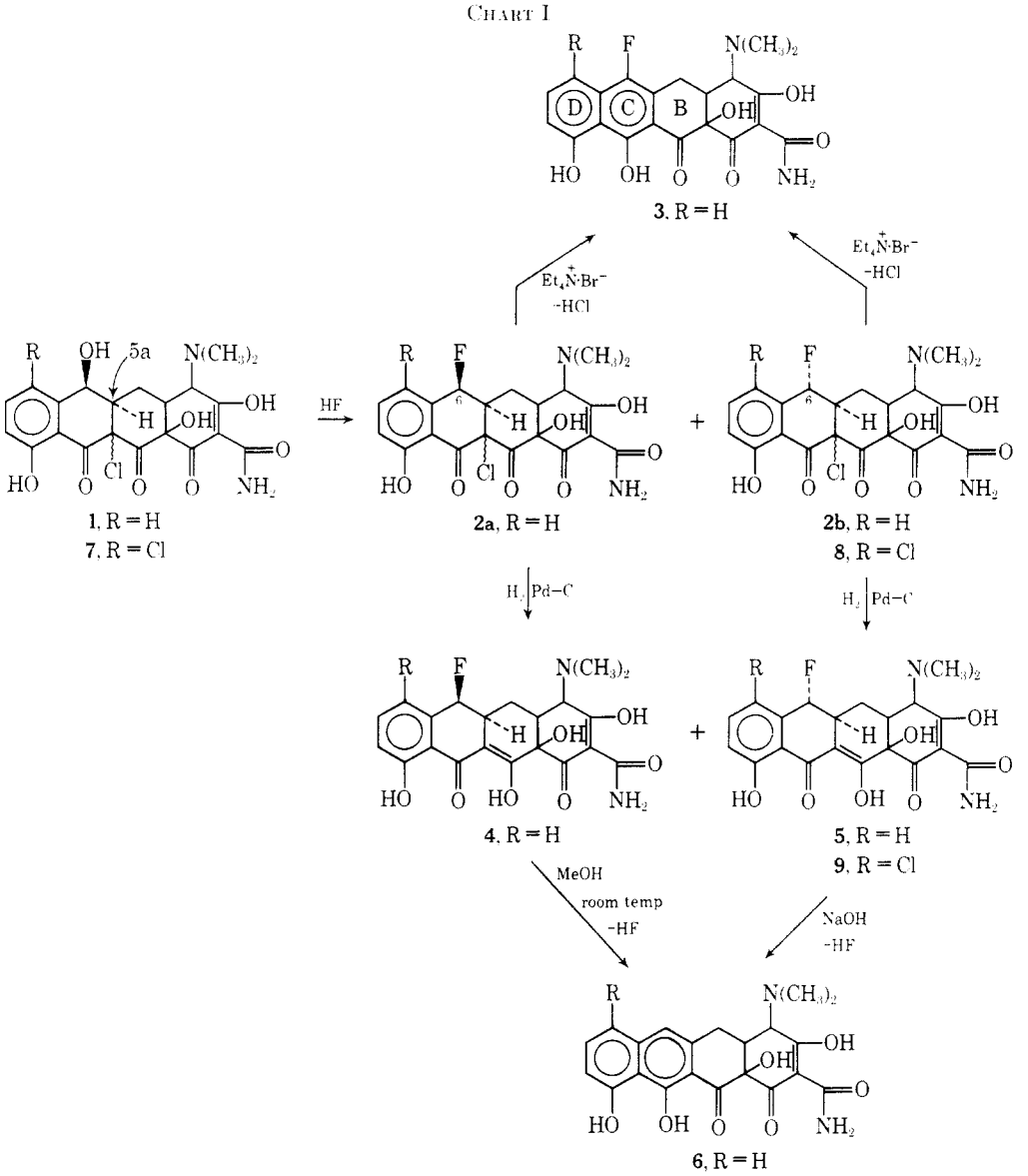


(3) Base treatment of tetracycline yields isotetracycline.



(4) (a) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **82**, 3381 (1960); (b) C. R. Stephens *et. al.*, *ibid.*, **80**, 5324 (1958).

CHART I

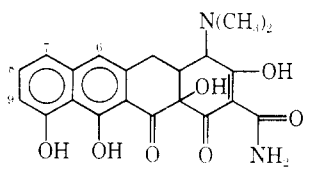


material **3** showed only the three aromatic protons in the D ring thereby locating the F at the 6 position.[5]

Mild catalytic reduction of the mixture of 11a-chloro-6-fluoro derivatives **2a,b** gave the two deschloro compounds **4** and **5** which could be separated by partition column chromatography. Although the exact stereochemistry of the F atom in **4** and **5** has not been determined, some indirect evidence is available for their tentative assignments. One of these isomers (**4**) loses HF easily at room temperature to give the known 5a(6)-anhydro-6-demethyltetracycline[6] (**6**). This unstable isomer **4** has been tentatively assigned the 6β-F configuration (a *trans* relationship relative to the 5a-H). The other more stable epimer **5**, which eliminates HF only on treatment with base, is then assigned the *cis* configuration (or 6α-F). Previous work in these laboratories has shown that the natural tetracyclines (6β-OH-5α-H) easily dehydrate to 5a(6)-anhydrotetracyclines but the 6-epitetracyclines (6α-OH-5α-H) dehydrate with extreme difficulty.[7]

An analogous reaction with 7,11a-dichloro-6-demethyltetracycline (**7**), followed by catalytic reduction yielded only the more stable 6α-F derivative **9**. Similarly, treatment of 7,11a-dichlorotetracycline (**10**) with HF afforded primarily the α-F derivative **11a** along with some of the 6-CH_2 derivative[8] **11b** (Chart II). Catalytic reduction of either of these compounds af-

(5) 5a,6-Anhydro-6-demethyltetracycline



shows an aromatic splitting pattern in the nmr as follows: the 7-proton is a doublet at 433 Hz, $J_{7,8}$ = 8 Hz; the 8-proton is a double doublet at 450 Hz, $J_{7,8} = J_{8,9}$ = 8 Hz; the 9-proton is a doublet at 410 Hz, $J_{8,9}$ = 8 Hz; and the 6-proton is a singlet at 426 Hz. The 6-fluoro compound **3** has the following aromatic splitting: the 7-proton is a doublet at 440 Hz, $J_{7,8}$ = 8 Hz; the 8-proton is a double doublet at 455 Hz, $J_{7,8} = J_{8,9}$ Hz; the 9-proton is a doublet at 414 Hz, $J_{8,9}$ = 8 Hz. The 6-proton is missing.

(6) J. S. Webb, R. W. Broschard, D. B. Cosulich, W. J. Stein, and C. F. Wolf, *J. Am. Chem. Soc.*, **79**, 4563 (1967).

(7) M. J. Martell, A. S. Ross, and J. H. Boothe, *ibid.*, **89**, 6780 (1967).

(8) R. K. Blackwood, J. J. Beereboom, H. H. Rennhard, M. Schach von Wittenau, and C. R. Stephens, *ibid.*, **85**, 3943 (1963). These authors reported a series of similar reactions with 11a-halotetracyclines but obtained only the 6-methylene derivatives.

CHART II

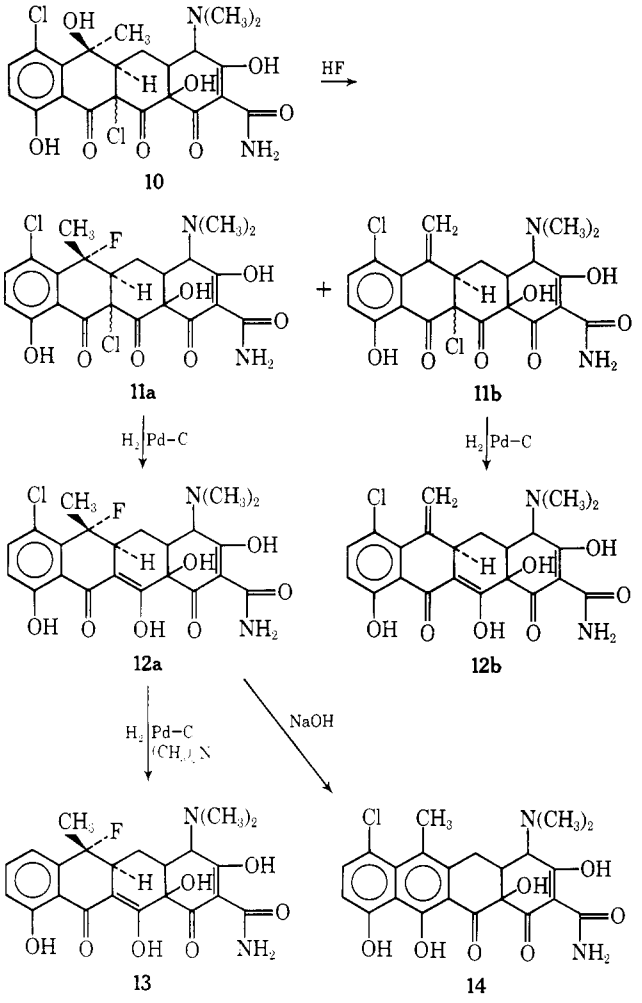
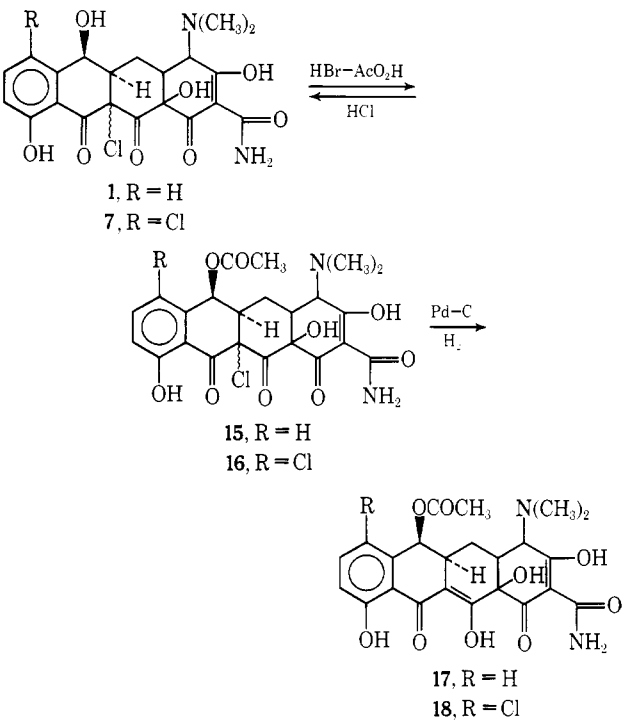


CHART III



forded the corresponding deschloro derivatives **12a** and **12b**. Further reduction of **12a** yielded **13**. Several attempts, under a variety of conditions, to catalytically reduce the 6-F group were unsuccessful.

When the 11a-chlorotetracyclines **1** or **7** were treated with HBr in AcOH, only the corresponding 6-acetoxy derivatives **15** and **16** were obtained (Chart III). In either case catalytic reduction removed the 11a blocking group to yield 6-acetoxy-6-demethyltetracycline (**17**) and 6-acetoxy-7-chloro-6-demethyl-tetracycline (**18**), respectively. The stereochemistry of the acetoxy group in **15** and **17** was confirmed by hydrolysis of **15** to the starting 11a-chlorotetracycline **1**.

TABLE I

In Vitro ACTIVITIES COMPARED TO TETRACYCLINE[a]

Deriv. of tetracycline	% act.
Tetracycline	100
6-Demethyl-6-deoxy-6-α-fluoro-	200
6-Demethyl-6-deoxy-6-β-fluoro-	12
7-Chloro-6-deoxy-6-α-fluoro-	400
6-Deoxy-6-α-fluoro-	30
7-Chloro-6-demethyl-6-deoxy-6-α-fluoro-	13
6β-Acetoxy-7-chloro-6-demethyl-	200
6β-Acetoxy-6-demethyl-	63

[a] Activities were measured turbidimetrically against *Staphylococcus aureus* by the method of E. Pelcak and A. Dornbush, *Ann. N. Y. Acad.*, **51**, 218 (1948).

Experimental Section[9]

All nmr spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent. Liquid–liquid partition chromatography[10] was carried out on neutral (acid-washed) diatomaceous earth.

11a-Chloro-6-demethyl-6-deoxy-6-fluorotetracycline (2).—In a polyethylene flask containing the 11a-chloro-6-demethyltetracycline[12] (6.5 g, 14 mmoles) there was added anhydrous HF (80 ml) and $MeSO_3H$ (5 ml). The solution was stirred in an ice bath for 1 hr and the HF was then evaporated under N_2. The solution was diluted with MeOH (15 ml) and the mixture was poured into a flask containing anhydrous $(Et)_2O$ (600 ml) with good stirring. The precipitated solid was stirred for an additional 0.5 hr and isolated by filtration; yield 7 g. The crude product was purified by partition column chromatography using the system C_7H_{16}–EtOAc–MeOH–H_2O (60:40:15:6). The α isomer **2b**, $\lambda_{max}^{0.1\ N\ HCl}$ 269, 348 mμ (log ε 4.23, 3.68), was collected between the second and fifth hold-back volumes and the β isomer **2a**, $\lambda_{max}^{0.1\ N\ HCl}$ 268, 350 mμ (log ε 4.29, 3.67), was collected between the sixth and thirteenth hold-back volumes. Both compounds eliminated HCl during mass spectrometry to give M^+ 430.

5a,6-Anhydro-6-demethyl-6-fluorotetracycline (3).—A solution of 100 mg (0.214 mmole) of **2** (α or β) and 28 mg (0.134 mmole) of $(Et)_4NBr$ in 30 ml of MeCN was prepared at room temperature. The solution was refluxed for 1 hr and then evaporated to dryness. The product was purified by partition chromatography using the system C_7H_{16}–EtOAc–MeOH–H_2O (70:30:17:4). It was collected between hold-back volumes 0.43 and 1.6; $\lambda_{max}^{0.1\ N\ HCl}$ 268, 420 mμ (log ε 4.81, 4.14); M^+ 430. *Anal.* ($C_{21}H_{18}FN_2O_7 \cdot 3H_2O$) F. See ref 5 for nmr.

6-Demethyl-6-deoxy-6-fluorotetracycline (4 and 5).—A mixture of the α- and β-fluoro compounds (200 mg) obtained above before column chromatography was dissolved in 20 ml of monoglyme and the solution was mixed with 100 mg of 10% Pd–C catalyst. The mixture was reduced for 5 min at atmospheric pressure and room temperature and the catalyst was filtered. The filtrate was concentrated to about 3 ml and diluted with MeOH and the pH was adjusted to 4.8 with Amberlite IR-45 anion-exchange resin.[11] The resin was filtered off and the filtrate was evaporated to dryness. The crude product was purified by partition column

(9) Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within 0.4% of the theoretical value.

(10) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Polletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(11) A weakly basic, polyamine (polystyrene) anion exchange resin of medium porosity, purchased from Mallinckrodt Chemical Works.

chromatography using the system C_7H_{16}–EtOAc–MeOH–H_2O (70:30:17:4). The unstable 6-β-fluoro derivative **4**, $\lambda_{max}^{0.1\ N\ HCl}$ 265, 370 mμ (log ε 4.21, 3.8), was collected between the 2.4 and 3.9 hold-back volumes and the 6-α-fluoro isomer **5**, $\lambda_{max}^{0.1\ N\ HCl}$ 268, 350 mμ (log ε 4.39, 4.19), between 3.9 and 6.1 hold-back volumes.

Both of these materials yielded the known 5a,6-anhydro-6-demethyltetracycline[6] (**6**) when treated with NaOH. The β-fluoro epimer **2a** gave the anhydro derivative immediately while the α epimer gave it only on standing in 0.1 *N* NaOH for 10–15 min.

7-Chloro-6-demethyl-6-deoxy-6-fluorotetracycline (9). Step 1. 7,11a-Dichloro-6-demethyl-6-fluorotetracycline (8).—A solution of 2.6 g of 7,11a-dichloro-6-demethyltetracycline[12] in 37 ml of liquid HF and 2.6 ml of $MeSO_3H$ was stirred in an ice bath for 1.5 hr. HF was then evaporated under N_2, the remaining $MeSO_3H$ solution was diluted with 5 ml of MeOH, and the mixture was poured into 1 l. of anhydrous Et_2O with good stirring. The precipitate was filtered and dried; yield 3.0 g. This material was purified by partition column chromatography using the system C_7H_{16}–EtOAc–MeOH–H_2O (60:40:15:6). The product was obtained in the 2.5–7.5 hold-back volumes. This material was used directly in the next step.

Step 2.—The product from step 1 (1.2 g) was dissolved in 30 ml of monoglyme and the solution was mixed with 600 mg of 10% Pd–C catalyst. The mixture was reduced for 20 min at atmospheric pressure and room temperature. The catalyst was filtered and the filtrate was evaporated to dryness. The product, purified by partition column chromatography using the same system (60:40:15:6), was obtained in the 0.75–2 hold-back volumes; $\lambda_{max}^{0.1\ N\ HCl}$ 263, 370 mμ (log ε 4.24, 4.09). The nmr of this material showed the C-6 doublet at 343 Hz with a J_{HF} of 50 Hz. *Anal.* ($C_{21}H_{20}ClFN_2O_7$) Cl, F.

7-Chloro-6-deoxy-6-fluorotetracycline (12). Step 1. 7,11a-Dichloro-6-deoxy-6-fluorotetracycline (11).—A solution of 6.0 g of 7,11a-dichloro-6-deoxytetracycline[12] in liquid HF (75 ml) was stirred in a polyethylene flask at ice-bath temperature for 3 hr. HF was evaporated by a stream of N_2. The remaining wet product was mixed with 5 ml of MeOH and the solution was poured in $(Et)_2O$ (1 l.) with good stirring. The precipitate was filtered and dried to afford 5.0 g of crude product.

Step 2. Catalytic Reduction.—The product from step 1 (2.0 g) was dissolved in 50 ml of monoglyme and the solution was mixed with 1.0 g of 10% Pd–C catalyst. The mixture was reduced for 30 min at atmospheric pressure and room temperature and the catalyst was filtered. The filtrate was concentrated to about 3 ml and diluted with 100 ml of MeOH, and the pH of this solution was adjusted to 5.0 with 6 *N* NaOH. Some precipitated solid was filtered off and the filtrate was evaporated to dryness; yield 1.5 g. This material was purified by partition column chromatography using the same system (70:30:17:4) and was collected at the 4.8–8.5 hold-back volumes; $\lambda_{max}^{0.1\ N\ HCl}$ 263, 370 mμ (log ε 4.24, 4.06). The nmr of this material showed the 6-Me doublet at 85 Hz with a J_{CH_3F} of 20 Hz; M^+ 480. *Anal.* ($C_{22}H_{22}ClFN_2O_7 \cdot 2H_2O$) F.

A second product isolated during the partition chromatography was identified as the 7-chloro-6-deoxy-6-demethyl-6-methylenetetracycline[8] (**12b**), $\lambda_{max}^{0.1\ N\ HCl}$ 245, 348 mμ (log ε 4.27, 3.98).

Further catalytic reduction of **12a** in the presence of 1 equiv of Et_3N yielded the 7-deschloro compound **13**: $\lambda_{max}^{0.1\ N\ HCl}$ 267, 353 mμ (log ε 4.24, 3.89); M^+ 446.

6β-Acetoxy-7-chloro-6-demethyltetracycline (17). Step 1. 6β-Acetoxy-7,11a-dichloro-6-demethyltetracycline (15).—A solution of 3.6 g of 7,11a-dichloro-6-demethyltetracycline[12] in 95 ml of a 32% HBr in AcOH was stored at room temperature for 2 hr. The solution was poured into 1 l. of anhydrous Et_2O with stirring. The product that separated was filtered, dried, and used directly in the next step; yield 3.6 g, M^+ 504, *i.e.*, the calculated molecular weight minus HCl.[13]

Step 2.—The product from step 1 (1.5 g) was dissolved in 25 ml of monoglyme and the solution was mixed with 700 mg of 10% Pd–C catalyst. The mixture was reduced for 75 min at atmospheric pressure and room temperature and worked up as before. The residue was dissolved in MeOH and the pH was adjusted to 4.2 with Amberlite IR-45 resin.[11] The resin was filtered and the filtrate was evaporated to dryness. The product, purified by partition column chromatography using the same solvent system (50:50:17:4), was collected at the 0.75–3.7 hold-back volumes; $\lambda_{max}^{0.1\ N\ HCl}$ 268, 370 mμ (log ε 4.20, 3.93). The nmr showed the CH_3CO at 111 Hz. *Anal.* ($C_{23}H_{23}ClN_2O_8$) C, H, Cl, N.

6β-Acetoxy-6-demethyltetracycline (16). Step 1. 6β-Acetoxy-11a-chloro-6-demethyltetracycline (14).—The 11a-chloro-6-demethyltetracycline[12] (3.0 g) was dissolved in 90 ml of a 32% HBr–AcOH mixture and the solution was stirred at room temperature for 3 hr. It was poured slowly into 1 l. of $(Et)_2O$ and the precipitated solid was filtered, washed well with $(Et)_2O$, and dried; yield 2.85 g. This material was purified by partition column chromatography using the same solvent system (1:3:1:2). The product was collected at 0.8–2.3 hold-back volumes; M^+ 506.

Step 2.—The product from step 1 (250 mg) was dissolved in 15 ml of monoglyme and the solution was mixed with 100 mg of 10% Pd–C catalyst. The mixture was reduced for 10 min at atmospheric pressure and room temperature and worked up as before; yield 185 mg. This material was purified by partition chromatography using the same system (50:50:17:4). The product was collected at 1.5–3.2 hold-back volumes; $\lambda_{max}^{0.1\ N\ HCl}$ 269, 364 mμ (log ε 4.20, 4.15); nmr 110 Hz (CH_3CO). This material (20 mg) was dissolved in 2 ml of 2 *N* HCl acid heated on a steam bath for 1 hr. The pH of the solution was adjusted to 5.0 and evaporated to dryness. The residue was purified by partition column chromatography using the same system (1:3:1:2). This was identical in all respects, *i.e.* uv, ir, paper chromatography, and biological activity, with 11a-chloro-6-demethyltetracycline (**1**).

Acknowledgements.—The authors wish to thank Mr. L. Brancone and staff for the microanalysis, Mr. G. Morton for the nmr spectra, Mr. A. Dornbush for the *in vitro* testing, and Dr. J. Karliner for the mass spectra.

(13) This peak at 504 probably resulted from the anhydro derivative ii.

i ii

(12) R. K. Blackwood, G. Ferry, H. H. Rennhard, J. J. Beereboom, and C. R. Stephens, U. S. Patent 3,109,007 (Oct 29, 1963).